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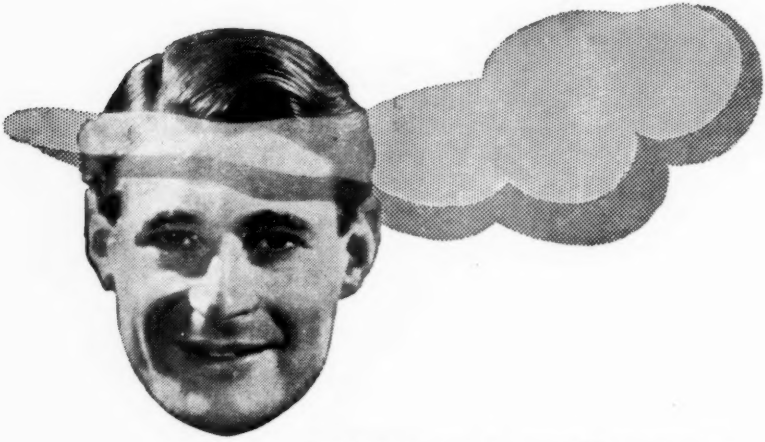

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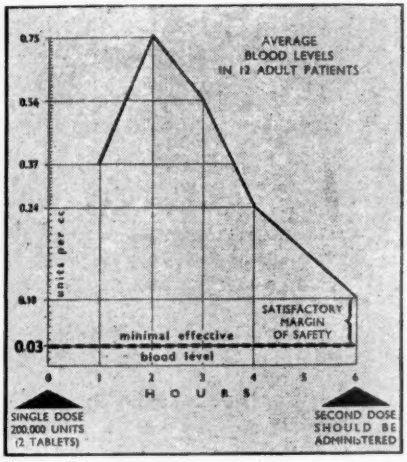

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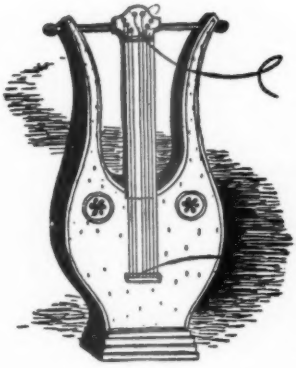

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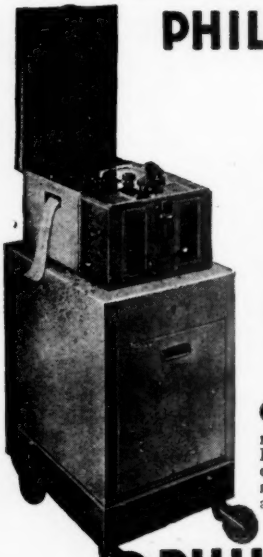

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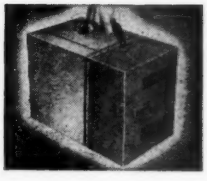

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Section of Ophthalmology

President—HUMPHREY NEAME, F.R.C.S.

[*February* 11, 1954]

(*continued from June* Proceedings, *p.* 481.)

Iridoschisis.—P. D. TREVOR-ROPER, F.R.C.S.

A fairly typical case of iridoschisis in a woman aged 63.

Both eyes had been blind and painful at the age of 15 (presumably an interstitial keratitis, as her W.R. was positive), and then at the age of 27, accompanying a pregnancy toxæmia, the eyes became blind again, and only the right vision returned after delivery. During the last three months her right vision had gradually and painlessly deteriorated, leaving only a 6/60 vision with a myopic correction in a small central field. The left eye had bare perception of light.

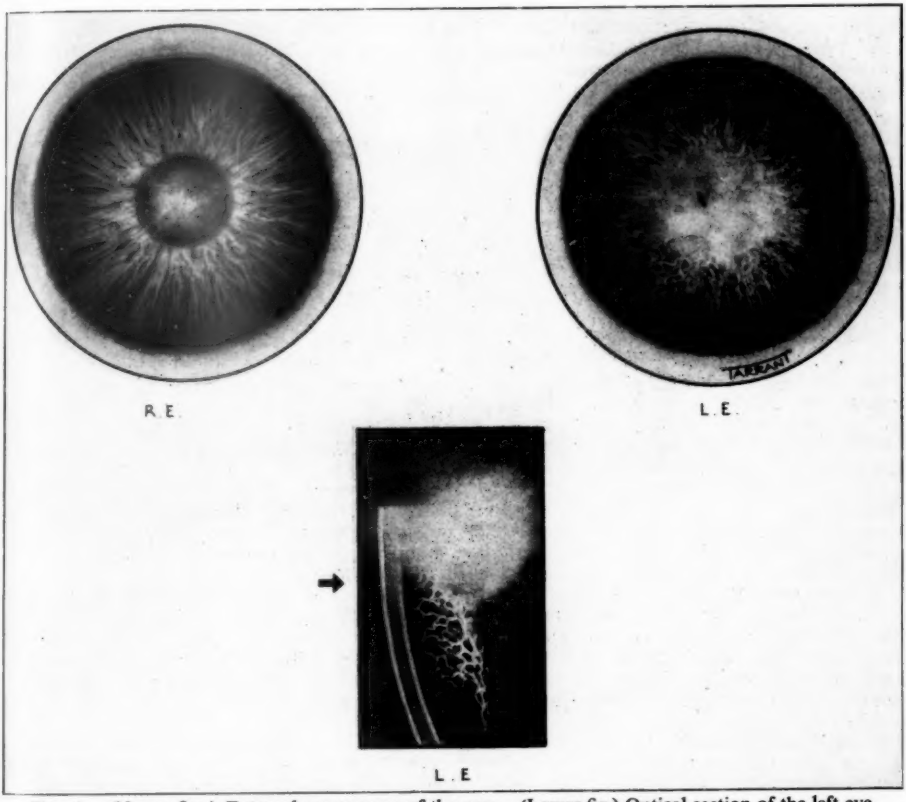

FIG. 1.—(Upper figs.) External appearance of the eyes. (Lower fig.) Optical section of the left eye, showing the iris stroma fluffing forwards to make contact with the cornea.

Both corneæ bore a diffuse axial opacity, with thickening of the corneal substance, superficial vascularization and a very occasional deep corneal vessel. Both irides showed a gross atrophy of the anterior layers, only the sphincteric regions being relatively intact; elsewhere the surviving dilator fibres and vascular sheaths were interspersed with radial lacunæ through which the slaty posterior layers could be seen. Even the shrivelled fibres that had survived were beginning to break up and fluff forward into the anterior chambers, as if teased out with a crochet hook; a process which was so advanced in the left eye that these residual tags made contact with the cornea over all but the peripheral ring where the atrophy was virtually complete. The pupils were central with a small regular light reflex. The right optic disc showed deep atrophic cupping (the left disc was concealed). Gonioscopy

showed broad anterior synechiæ, with heaping up of the degenerative iris fibres in the angles (Mr. H. E. Hobbs). The tension varied between 55 mm.Hg and 80 mm.Hg, being slightly alleviated by atropine but not by eserine. (Since showing the case a cyclodiathermy has been performed, and the tension is now fairly well controlled but vision continues to deteriorate.)

The appearance of the irides in this case closely resembles all the other 13 reported. Iridoschisis is generally believed to be a dystrophic change, occurring bilaterally in old people, with a corneal dystrophy sometimes accompanying it. It has also occurred in younger patients unilaterally after a blunt trauma; and in the above case it would appear that the initiating factor in the iris degeneration was the recurrence of a uveitis during pregnancy after a severe interstitial keratitis some years previously. The glaucoma is probably secondary to the mechanical impediment to drainage, and not a primary cause of the iris atrophy, since the hypertension was arrested by treatment in 2 of the reported cases, yet the iris changes remorselessly progressed. There was thus little prospect of effective treatment.

The President said that this condition was extremely rare; he had never seen anything like it before.

Mr. H. E. Hobbs recalled the case of a woman aged 40 in whom a similar condition of the iris was to be seen. It had presented first at the age of 10 with raised tension and a cupped disc; but neither the iris atrophy nor the glaucoma had progressed during the intervening period following corneoscleral trephining.

Mr. Trevor-Roper said that a series of cases had been reported since the condition was named by Loewenstein and Foster in 1945 (*see* References).

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[*May* 13, 1954]

A FURTHER REPORT ON THE RESPONSE OF MACULAR DISEASE TO TREATMENT WITH CORTISONE AND ACTH

I

Case Reports—Mr. W. E. S. Bain

Our interest in the effect of cortisone upon macular disease was stimulated by the unexpected response in a case brought before this Section in November 1952 (Hobbs, H. E., 1953, *Proceedings*, **46**, 213): and for the past two years or so we have been treating cases referred to us by surgeons of the Moorfields, Westminster and Central Eye Hospital of which the single common feature has probably been that the macula has been involved by retinal disease.

Most of these cases, and certainly most of the cases we have undertaken to treat, have exhibited lesions which appeared to be exudative, appearances suggestive either of œdema or of denser and harder exudates. One or two of them may well have been inflammatory, and a few others were likely, from their appearance, to have been fibrotic lesions or simple degenerations. Establishment of the causes of these various lesions formed no part of our investigations.

In some cases, e.g. central serous retinopathy, the history from an intelligent subject may be the most valuable guide to the condition; in others the fundus appearances may be characteristic, more especially when the binocular ophthalmoscope is available and can be supplemented by slit-lamp microscopy of the fundus. On the other hand, most of these lesions give rise to field defects, and when these can be elicited they provide useful evidence for later comparison during treatment. In general all of these methods of examination have been employed to assess the initial lesion and its progress during treatment.

Though these cases form a heterogeneous group, the type of exudate seen in the fundus does appear to bear some relation to the response to treatment. We have, therefore, divided the cases broadly into two groups showing respectively œdematous types of lesion, and denser, harder exudates.

Treatment, in general, was by twice-weekly injections of 0·4 c.c. cortisone, administered at first subconjunctivally, but later into Tenon's capsule with the addition of 1,000 units of hyaluronidase, since the addition of this spreading factor appears to make the injections slightly more effective.

Cortisone tablets by mouth (twice or thrice daily for one or two weeks) have also been used, commonly as a form of maintenance therapy following the more intensive treatment by injection, in an attempt to prevent the relapses seen in one or two earlier cases. One or two cases have been treated with ACTH.

ŒDEMATOUS LESIONS

There are 15 cases in this group. In 10 of them the fundus appearance was that of pre-retinal œdema, i.e. there was an area of glistening fluid, usually limited by a clear ring reflex. In most of them the subjective disturbance was only moderate, visual acuity being reduced to 6/18 at worst and in most cases being in the region of 6/9 or 6/12. "Blurred vision" was universally noted and in some cases

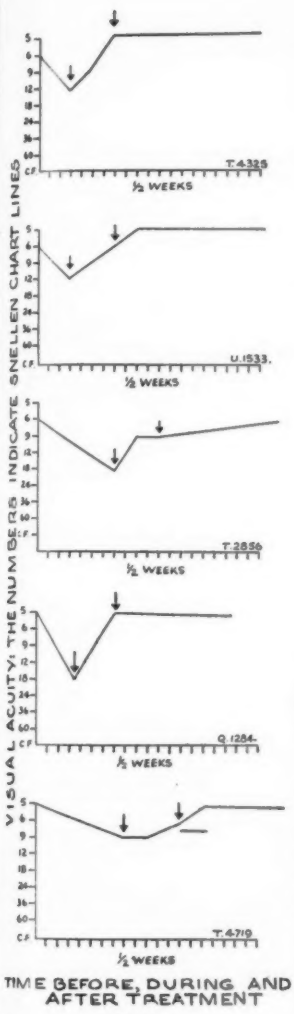

FIG. 1.

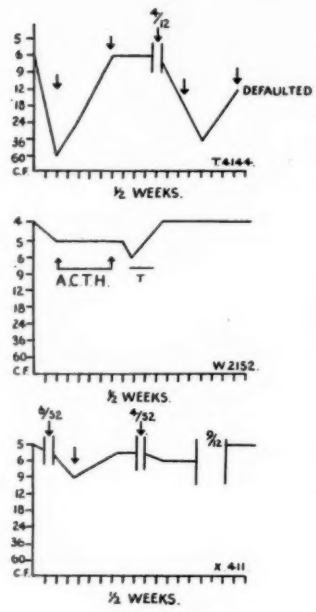

FIG. 2.

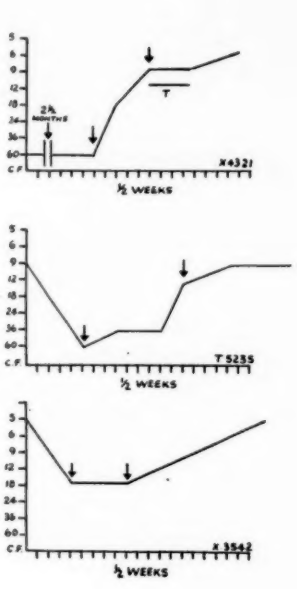

FIG. 3.

"yellow vision" or a "purple ring around vision" had been a presenting symptom. Visual field defects were, in general, inconclusive and, although scotomata were plotted in some cases, the fields did not provide a reliable means of recording the defect.

In five cases there was a prompt response with improvement of visual acuity and reduction of subjective disturbance either during or immediately following treatment (Fig. 1).

In three others (Fig. 2) after initial improvement a relapse occurred. One of these (W.2152), who relapsed at once when treatment ceased, responded rapidly to further treatment with cortisone tablets; the second (X.411) was seen four weeks after the end of the course of treatment, and further injections produced little effect. The condition improved gradually under treatment with other medicaments during the following nine months. In the third case (T.4144) the relapse occurred four months after treatment had been followed by recovery, and at this time a raised disc of yellowish exudate was apparent close to the macula. Further treatment was incomplete as the patient defaulted; but improvement of from 6/36 to 6/12 was seen after the first four injections. An interesting point in this case is the fact that, as in other cases with a more solid exudate, there was an initial fall in vision during treatment (6/18 to 6/36) before improvement began.

In 3 cases a para-macular hole (confirmed by slit-lamp microscopy) presented surrounded by a disc of œdema, and although under treatment the œdema rapidly disappeared, the hole remained and vision was little affected.

Another case in this group serves chiefly for comparison: it is that of a man in whom the local reaction to injections was sufficiently disturbing to warrant their cessation. Spontaneous recovery took place during the succeeding three months.

The remaining 3 cases showed instead of a disc of pre-retinal œdema a featureless, dark and slightly swollen macula and this was accompanied by a greater reduction in vision than in the preceding cases. This we have interpreted as being due to intra-, rather than pre-retinal œdema. Coloured visual disturbances have been noted at the onset in these cases; but have soon been overshadowed by the general blurring of vision.

All 3 of these cases have done well (Fig. 3); although some residual disturbance of vision as metamorphopsia or micropsia remains. In one of them the fellow eye had suffered a similar

disturbance ten years previously which, after a protracted course, had terminated in a scarred, pigmented macula, with vision of only finger counting.

As would be expected from the minimal fundus disturbance seen in all of these œdematous lesions, the retinal changes during treatment have not been remarkable. It has been possible, however, in several cases of pre-retinal œdema to see during the early days of treatment a spreading out of the œdematous disc, the margins of which became indistinct; and this change, which coincided with the early improvement in symptoms, occurred in some cases in which the duration before treatment had been a matter of several weeks. No such alteration was seen in the three cases of intra-retinal œdema, in which the macular swelling appeared simply to subside leaving a small area of fine pigmentary disturbance.

Although many of these cases recover completely spontaneously it seems generally agreed that the longer the œdema persists the more likely is permanent impairment of vision. We would suggest that cortisone may, by cutting short the period of œdema, reduce the number of cases with permanently reduced vision.

Lesions with Denser Exudates (9 Cases)

Among the more solid types of exudate there was, of course, a considerable variety of lesions; all of them, however, are of a type which is expected to run a longer course than the œdematous ones, and where any improvement with treatment has been seen this has been a good deal slower than in the previous group. Nevertheless, the type of response in individual cases suggests that treatment with cortisone has modified the course of the disease.

Four cases are considered together first because they seem to provide a link with the œdematous lesions already referred to. In them the lesion at, or close to the macula, appeared as a circumscribed disc consideraby smaller than the optic disc, and having the appearance of a cyst. This cyst, however, was seen to be distended with opaque pinkish fluid and presented a quite different picture from the serous cyst seen with purely œdematous conditions.

Case I.—Male aged 51, with the swelling at the macula. Vision, which had been failing for a month was reduced to 6/60 when we first examined him, and there was a small central scotoma. The fellow eye showed no abnormality. Improvement here began at once with treatment, and after two injections, visual acuity was 6/24, the lesion was less clearly visible, and the absolute part of scotoma, which had increased somewhat in size, had moved above the macula. After a further three injections vision had improved to 6/12, very little fundus disturbance was visible, and the field defect was reduced to minute dots above fixation. Treatment was continued to a total of 14 injections, when no abnormality was detectable in field or fundus, and vision, although some metamorphopsia persisted, was 6/9. In the succeeding year improvement to 6/5 has been seen and maintained.

Case II.—Male aged 66. Here the history was less clear. Vision in the left eye, which had been failing for some time, was 6/24 corrected, the fundus showed a similar appearance to that of the last case, and the field a central scotoma. Observation in this case was hindered by the fact that the patient irritated to all mydriatics; however, after three injections vision was "somewhat better", and improvement continued so that after 7 injections it had reached 6/9. The fundus at this time showed still a small disc of exudate, but above and nasal to the macula. Cortisone tablets were given as maintenance therapy for a further two weeks, and since the end of treatment, 7 months ago, recovery has been maintained. Comparison with the fellow eye in this case is of interest since deterioration had begun in a similar fashion some years ago, but vision in this eye was reduced to 6/36, with a scarred atrophic macula.

Case III.—Woman aged 62 in whom, also, the fellow eye had failed several years previously. In it vision was reduced to finger-counting, and the fundus showed an incomplete ring of hard, yellowish exudate at the macula itself. Vision in the good eye had recently become a little blurred and was 6/9 when she was first examined; the fundus showed a similar disc of exudate just above and nasal to the macula, and a centro-cæcal scotoma involved fixation. Treatment was by intra-tenon cortisone and hyalase injections to a total of 8, and early in the course there appeared clear gaps in the general blur before the vision at a time when the disc of exudate was less clearly defined and fluid appeared to be spreading out over the surrounding retina. When treatment was discontinued no fluid was visible; but below the macula was an incomplete ring of hard yellowish exudate. Vision was 6/6 slowly, with some metamorphopsia.

Case IV.—Woman aged 33 with a history of blurred vision for three weeks. Visual acuity was 6/6, and the disc of exudate did not involve the macula. Injections were not tolerated and treatment with ACTH to a total of 500 mg. was quite ineffective. Vision in this case has remained good; but the cyst has recently become a hole.

The two following cases are distinguished from the foregoing group because in them the fundus disturbance appeared as a slightly raised yellowish nodule just off the macula with surrounding œdema involving the fovea.

Case V.—A man aged 47. He had noticed a black spot just off centre for a month and vision was 6/12. Treatment was by injections followed by tablets, and after the first two injections vision fell to 6/60; but improved during the next week with continued treatment to 6/24, and after a further week was 6/9 plus. The fundus meanwhile had shown flattening of the exudate. Since this time, six months ago, vision has been maintained and slight pigmentation of the lesion has appeared (Fig. 4).

Case VI.—Man aged 33 whose fellow eye had failed five and a half years previously. He was considered at first to be afflicted with central serous retinopathy, but later developed changes of a senile exudative type, and vision finally deteriorated to 6/36 with a scarred atrophic macula (Fig. 5). In the recently affected eye, blurred vision had been noted for four days, but was still 6/6, and the macula is illustrated in Fig. 6. Treatment was

again by injections over a period of four weeks, and the lesion progressively cleared with improvement of vision to 6/4 at the end of the second week. This improvement has been maintained over a period of six months, and during this time some fine pigmentation of the macular region has appeared.

In the foregoing cases progress to date has been satisfactory. In two others, however, initial improvement has been followed by relapse, and, in them, the fundus lesions seen at some time in the course were somewhat similar. They appeared as ovoid translucent swellings at the macula, in which distinct flecks of black pigment could be discerned (Fig. 7).

Case VII.—Woman aged 73. The right eye had failed many years previously, and showed an old pigmentary lesion at the macula (Fig. 8), vision being reduced to finger counting. In the left eye vision had been less clear for some six months and when she was first examined was reduced to 6/36.

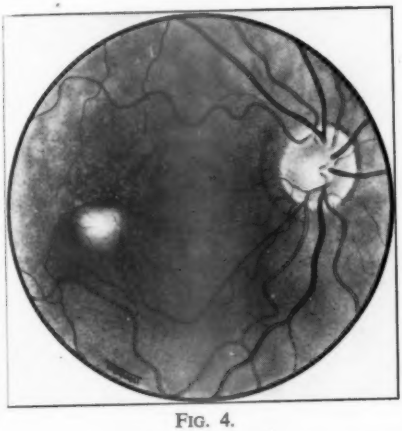

FIG. 4.

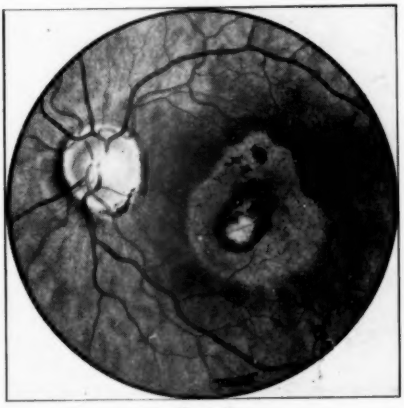

FIG. 5.

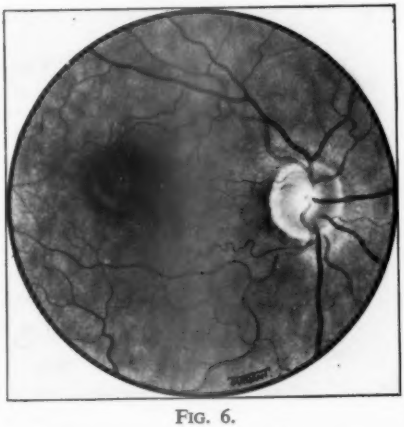

FIG. 6.

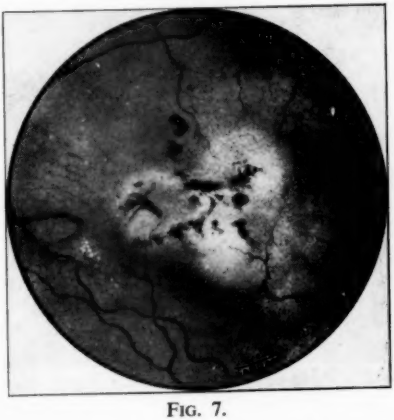

FIG. 7.

After four injections there was some visual improvement (to 6/24) and after six injections only a vague area of œdema with dispersed pigment flecks could be seen. Vision at this time was 6/6 with the addition of plus 1·5 dioptre sphere. This improvement was maintained for a period of nine months, when vision began to appear patchy, and within a week fell to 3/60 with the development of an ill-defined patch of white exudate at the macula. Intensive treatment was, unfortunately, without effect.

Case VIII (shown at meeting).—The comparable case arose in a hospital sister. In this instance the macular appearance referred to arose after a year and a half in which both maculæ have been affected by varying degrees of œdema. During this period there have been fluctuations of vision between 6/36 and 6/9 corresponding with variations in the degree of œdema, upon which treatment has been only moderately effective. It seemed likely that this was because she had found difficulty in continuing treatment regularly and when she reappeared, therefore, some four months ago with vision reduced to 6/18 in each eye we were prepared to accept the condition as a relapse. Refraction at this time, however, showed that with the addition of a plus 2 dioptre sphere 6/9 vision in each eye could be obtained. Since that time a relapse in the right eye seems to have set in.

Case IX (shown at meeting).—The last case which has responded to treatment is that of a man aged 41

with a large yellow exudate extending from the disc above the macula. The appearance of the fundus when he was first seen a year ago is shown in Fig. 10 and it will be seen that the lower edge of the exudate consisted of fine dots which overlay the macula. Vision at this time could not be improved beyond 6/60, and although the condition appeared to offer little chance of improvement a course of injections was undertaken after consultation with Mr. P. McG. Moffatt, whose patient he was. We were somewhat sceptical of the symptomatic improvement which he claimed (6/24 after two injections); but when after five injections he read a good 6/18, it was apparent, also, that the lower edge of the exudate showed fewer of the punctate deposits. After seven injections he claimed that his vision had returned to normal and could read 6/12 and this absorption of the fine exudates continued to the final state shown in Fig. 11. Vision during the succeeding year has been maintained.

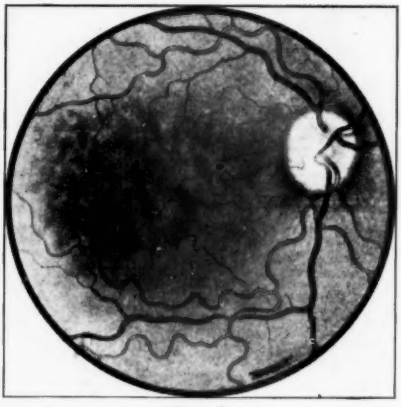

FIG. 8.

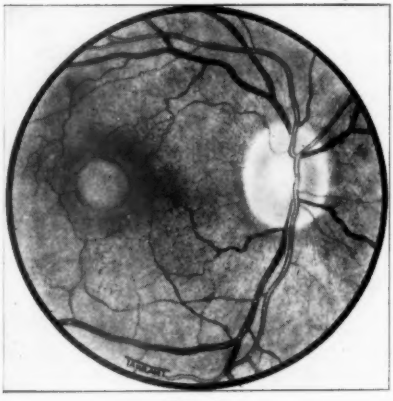

FIG. 9.

FIG. 10 (*Case IX*).—Exudative macular degeneration. L.E. 24.3.53.

FIG. 11.—Same case. L.E. 30.7.53. Note the absorption of much of the fine exudate at the edges of the lesion.

UNRESPONSIVE CASES

Fifteen cases have been grouped as unresponsive although in some of them symptomatic improvement has been claimed, and at times recorded, and in some of them alteration of the fundus lesion under treatment has been seen (Table I).

TABLE I

	No. of cases	Slight response	No response
Active exudative lesions with hæmorrhages ..	2	1	1
Obstructive vascular lesions	2	–	2
Cystic degeneration	2	–	2
"Pigmentary degeneration"	1	–	1
Visual disturbance and colloid spots	3	–	3
Disciform lesions	3	–	–
Myopic degeneration	2	1	1

Disciform Lesions

Three cases (Nos. X, XI, XII). All gave a longish history, between six months and three years, and all appeared to have clear-cut discs of firm exudate at the macula, e.g. Fig. 9. No alteration under treatment was seen.

Active Exudative Lesions with Hæmorrhages

Two cases.—Both of these cases showed œdematous swellings at the macula with a certain amount of superficial hæmorrhage.

In the first (Case XIII) no change was seen after injection treatment alone, and although it is possible that systemic treatment, which we were not able to use at this time, might have influenced the course of the lesion, later experience suggests that the presence of the hæmorrhages is of bad prognostic significance.

The second (Case XIV, shown at meeting) is still under treatment. Her left eye failed some three years ago and vision is reduced to hand movements with a scarred lesion at the macula. Metamorphopsia had become apparent in the right eye two or three weeks before we first saw her, and the fundus showed then a central area of œdema with surrounding hæmorrhages. Since that time, some six months ago, she has been almost continuously under treatment, at first with combined ACTH and intra-tenon injections. After three months vision had improved to 6/6 with localization of the œdema to a disc on the nasal side of the fovea. At this time fewer hæmorrhages were visible, but there was some extravasated blood close to the macular lesion. More recently there has been a relapse with vision reduced to 6/24 and extension of the cystic swelling. Although she has noticed some subjective improvement during the last week or two, we are not hopeful of the outcome.

Obstructive Vascular Lesions

Two cases.—In the first (Case XV) obstruction of the central retinal artery had been present for three days, and the chances of improvement by any treatment were considered to be poor. The patient was willing to undergo injections, and 7 were given—without effect. The second (Case XVI) showed a small area of œdema at the macula with scattered surrounding hæmorrhages, and the diagnosis of infective thrombosis had been made. Treatment was undertaken in an effort to limit the spread of the lesion, but was quite ineffective.

Cystic Degeneration of the Macula ("Honeycomb Macula")

Two cases (Nos. XVII and XVIII).—One of these had noted symptoms for only four months, the other for four years. Treatment was without effect on either.

Myopic Degeneration

Two cases (Nos. XIX and XX).—Both of these showed an appearance suggestive of exudate as well as the characteristic myopic degeneration. In the first no change was seen with treatment; but in the second vision improved from 6/60 to 6/12; little alteration could be seen in the fundus.

Pigmentary Macular Degeneration

Case XXI.—No change was seen.

Visual Disturbance Associated with Colloid Spots at the Posterior Pole

Cases XXII, XXIII and XXIV.—In all of these cases we presumed that degenerative retinal changes appearing coincidentally with the colloid were reponsible for the visual disturbance. In the first hard, perimacular exudates suggested that treatment might produce some effect. A comparable appearance in the left eye of the second case was seen; but in the third case the worst eye showed only pigmentary degeneration. Treatment was without effect in all three cases, and the appearance of the colloid remained unaltered.

II

Discussion of Cases—Mr. H. E. Hobbs

In accepting these cases for treatment we were facing a difficult problem both in the classification of the cases themselves and the assessment of their progress. Pathological evidence of the cause and precise site of these lesions is hard to come by and diagnosis is therefore even more a matter of opinion than usual. The hypothesis upon which we based any hopes of successful results was the belief that cortisone and ACTH could be effective upon exudates in the retina and choroid and that they might in this way produce visual improvement. This hypothesis had been suggested by some published results of treatment and, in our own experience, by the case shown to the Section in November 1952 (1953 *Proceedings*, **46**, 213).

I should, therefore, perhaps, first say something about the further progress of this patient. (She was one of those who was examined at this meeting.) Exudate first appeared at the left macula towards the end of 1950 and at the right in June 1951 while she was under observation. She was under treatment up to November 1952. During the interval there has been very little change in vision, which remains 6/9 in the right and 6/36 in the left eye. The opaque pre-retinal tissue extending from the disc above the macula in the left eye shows signs of organization and in both eyes there is some pigment disturbance at the posterior pole with persistence of some of the hard yellow exudates. The

improvement, therefore, has been maintained, since at one time vision in each eye had fallen to 5/60. I should like to emphasize that the eye in which visual loss is apparent (the left) is that in which the duration before treatment is certainly several months; in the other eye (the right) where the lesion became apparent whilst under observation and was treated at once, there was full visual recovery, which has, so far, been maintained.

In describing this case I said that I hoped that further experience might enable one to decide with the ophthalmoscope which sort of macular lesion could be expected to respond favourably to this rather tedious and prolonged form of treatment; and since that time Mr. Bain and I have, largely through the courtesy of our senior colleagues at both branches of the Moorfields, Westminster and Central Eye Hospital, been able to make trials in a number of widely different cases, the majority of which have been included in Mr. Bain's survey.

We were concerned in the first place to verify the fact that treatment of this sort does produce an effect upon macular exudates: that this is so had been strongly suggested in the case to which I have just referred by the prompt alterations in vision, field defects and fundus appearance seen during treatment, and among the cases just described there are some others which confirm this suggestion. Assessment of these lesions and their progress is not a simple matter: the appearance of the fundus lesion itself, more especially when early, is not easy to agree upon; but here we have found the binocular ophthalmoscope provides some help and Fig. 7 is an illustration in which the artist was able to record the appearance of swelling seen with this instrument when it was doubtful with the monocular method. Visual fields should provide in these cases a more reliable estimate of the defect; but the very fact that central vision is affected means that fixation is difficult and accurate recording of the scotoma in the average case questionable. We had hoped that this might be overcome by employing stereofixation; but, unfortunately, the apparatus was not available for most of these cases. We have found campimetry useful in a number of cases, as has been demonstrated. Slit-lamp microscopy of the fundus with the Hruby or contact lens has proved very useful, especially in distinguishing between cysts and holes of the macula; and repeated refraction has, on several occasions, demonstrated that reduced vision was attributable not to macular damage but to an alteration in the optical conditions of the eye.

The œdematous lesions were so classified from the fundus appearance of clear œdema; but the quite different effects upon vision which are apparent in the various cases would appear to indicate that the lesions, although probably all œdematous, affected the retina in at least two distinct ways. Fluid which simply formed a film on the surface of the retina produced little visual loss, a vague scotoma and little or no metamorphopsia, but was apt to give rise to some colour disturbance during the time that it persisted. On the other hand, when no pre-retinal disc of œdema was apparent and the macula appeared dark, blurred and swollen, vision was more severely affected, there was a definite scotoma, and metamorphopsia, which became apparent as vision improved, was apt to persist to some extent. These latter we take to be cases of intra-retinal œdema in which the fluid may well be maximal in Henle's fibre layer at the macula. In one or two cases there appeared to be an increase in hypermetropia which such a collection of fluid might be expected to produce. Sometimes both sorts of lesion were seen in the same patient and an early history of coloured vision and slight blurring was followed by severe visual loss and a swollen, characterless macula.

All of these cases would probably be included by most surgeons under the heading "central serous retinopathy", the course of which is notoriously variable. The man whose fellow-eye lesion is illustrated in Fig. 5 serves as an example of this variability; for, although this lesion appeared at first to be a simple œdematous one, it resulted in a scarred atrophic-looking macula. Treatment of the recently affected eye has, so far, been successful; but it is obviously too early to say that this eye is not destined ultimately to follow the course of its fellow. Nevertheless the response to treatment encourages us to believe that such a course may be interrupted if it does threaten.

Two factors suggest that treatment is responsible for the improvement seen in these cases. The first is the fact that it has been seen to begin quite rapidly during the first week of treatment in some cases in which vision had remained low for several weeks; and the second is the occurrence of relapse. The role of treatment seems to be established in the cases in which relapse was seen at once when treatment was stopped and which responded rapidly to further treatment. The one case in which symptoms returned after a period of some four months may perhaps be more truly described as a recurrence rather than a relapse and the failure of treatment to affect it is thus more readily understood.

The disc of opaque pink exudate seen in the second group of cases seems to be an intermediate stage between these œdematous lesions and the hard exudates which follow them in some cases, and which present *de novo* in others. The fact that 3 of the 4 cases in this group showed a good deal of improvement under treatment suggests that they should be included as purely œdematous lesions. My limited experience of such lesions, however, is that they do not carry the good ultimate prognosis which may be expected from most cases of central serous retinopathy. They tend rather to deteriorate. The 2 cases in which disease of the fellow eye which was symptomatically similar in its onset terminated in an atrophic macula seem to support this view. There can be no doubt that the lesions may persist unaltered for quite a long time; but the possibility of the macula becoming involved by a very slight extension of the lesion is clearly a serious threat to central vision. The success of treatme

in these cases, even if it is temporary and may be difficult to repeat in a recurrence, is of importance since, as the example of the 1952 case shows, a period of years may intervene between relapses.

Since all of the foregoing types of lesion appear to be composed of fluid of a varying degree of turgidity, it is not difficult to postulate a simple vascular mechanism, provoked by the hormone treatment, whereby the exudates become absorbed. The more solid-looking, yellow exudates, however, at first sight seem to be very unlikely to respond in this way. Not many, of course, have been seen to respond; but I may perhaps recall again the 1952 case to be considered with others described by Mr. Bain. In the original case and in one or two of the more recent ones improvement in vision and field defect has been preceded by a pronounced deterioration of both and, during this time, there has been noted in the fundus a loss of clarity in the originally distinct exudate, followed by the appearance of œdema and some improvement in vision. Finally, as I have already mentioned, fine dots of yellow exudate have been seen to form at some distance from the macula, as though left there by a tide of fluid (1953, *Proceedings*, 46, 213, Figs. 2 and 4.) This sequence of events has been seen in only a few cases; but I have not seen it in any untreated cases and it has happened in the space of a few weeks. I think, therefore, that it is due to treatment and provides ophthalmoscopic evidence of the efficacy of cortisone on these lesions. It could be interpreted as an initial liquefaction of the solid exudate, followed by its absorption, or partial absorption. Whether this is the true explanation or not I do not know; but this idea does appear, at present, to provide a working hypothesis.

The chances of obtaining histological evidence of the precise situation and nature of the changes in these cases are extremely rare and none has presented to us. In the foregoing cases the ophthalmoscopic appearances have suggested that the exudates were either purely pre-retinal or that they penetrated the retina from the surface. In Cases VII and VIII, however, the behaviour of the lesions suggests that they lay deeper, either in the choroid, or possibly in Henle's layer of fibres. These were the cases in which the fundus picture was that of a raised translucent disc containing distinct pigment flecks (Fig. 7): in one of them the case presented in this way; vision under treatment improved from 6/60 to 6/6, although a later relapse has resulted in permanent loss of central vision. In the second (Case VIII) the disc appeared after a year under treatment, during which time the early appearance of œdema at the macula seemed at first to respond but later relapsed, to be followed by further improvement to a visual acuity of 6/9. In both of these cases the period of restored vision has been when the macular swelling was apparent and an addition of plus one and a half and of two dioptres, respectively, to the spectacle correction was called for. This suggests, I believe, that the collection of exudate lies in the deeper layers of the retina or behind it and the occurrence of dark pigment in the exudate is I think further evidence of this since it must surely be due to disturbance of the pigment layer of the retina. Treatment of these cases of deeper exudate has been only partially successful; but it can be said to have had a definite, if temporary, effect. It is to be hoped that means may yet be found to prolong this.

In Case IX (Figs. 10 and 11) these intermediate changes were not seen; but this may well be because in this case the absorbed exudate was already in the state of fine deposits which might be presumed to be more readily absorbable.

The Unresponsive Lesions

The unresponsive lesions were instructive. In the case of the "holes" and that of pigmentary degeneration the result has been rather what one would expect from the known permanently destructive nature of the lesions. We viewed the 2 cases of honeycomb macula somewhat more optimistically, hoping that they might respond in a fashion similar to the simple cysts; but there has been no improvement. The appearance of two of the disciform lesions suggested an organized, fibrotic condition and the lack of response in them was not surprising; but in the third (Fig. 9) the picture with the ophthalmoscope was sufficiently similar to the 1952 case to raise (vainly, as it proved) more hope of improvement.

The failure of this treatment to make any impression on the case of central retinal artery block will probably surprise no-one; but it seems likely from the course of the other cases grouped with it that where *any* degree of vascular damage is present, that is to say, if any hæmorrhages are associated with the exudate, then the prognosis is more gloomy. The unfavourable course of the man with an infective thrombosis of the macular vessels, to whom Mr. Bain has referred, and that of Mr. T. K. Lyle's patient who appeared here for examination with hæmorrhages and exudate (not illustrated) are offered as illustrations of this point. The further case (Case VII) in which improvement was followed by sudden and permanent relapse can also, I think, be most easily explained as the result of hæmorrhage.

In some cases colloid spots have seemed to alter a little during treatment; but in the 3 cases in which they were the most obvious lesion, 2 of which have appeared here, little or no visual change occurred. I think that this may properly be said to bear out the view, held by many, that visual changes in such cases are the result of parallel retinal degenerative processes and not of the colloid itself.

One of the myopes with retinal changes did show some visual improvement under treatment and we are unable to account for this, since the fundus changes appeared to be of the usual degenerative

type. One wonders, however, whether in this case there was present a cyst of the type which Coats described as occurring in myopic retinæ.

Treatment

We have aimed at getting the highest possible concentration of hormone as close as possible to the retina, and have therefore used systemic treatment to achieve this through the blood stream. We have the impression, however, that cortisone injected into Tenon's capsule is a little more effective, and more especially when hyaluronidase is added to encourage its diffusion. Recently a combination of these routes has been used to achieve a maximal concentration.

Conclusions

Clearly no firm conclusion can be drawn from this small series; but we do feel that some of the cases have confirmed the belief that cortisone can affect retinal exudates. It is evident, too, that hard exudates as well as œdema can be encouraged to absorb, and the retinal and field changes seem to suggest that they do so after passing through a stage of liquefaction. This treatment is, of course, no cure, but we believe that it can, if only temporarily, interrupt the course of some of these cases with exudates. The ophthalmoscopic distinction of cases likely to respond favourably remains difficult; but we have tried to throw a little more light upon it from our experience with these patients.

We should like to emphasize our gratitude to the surgeons who have entrusted us with the treatment of their cases and to record our appreciation of the help which we have received from the Department of Medical Illustration of the Institute of Ophthalmology in recording the fundus appearances.

The President said that the case with the dense mass of exudate (Case IX) seemed to him a retinopathy in the group described originally by Coats. It seemed that some benefit was obtained from cortisone. He would not imagine that there was any prospect of removing colloid bodies by cortisone; they were there permanently. On the other hand the lesions affecting the macula or the fovea itself might be different.

He asked whether it was essential that the patient should be hospitalized, or was there any danger in having these patients ambulatory?

Mr. C. A. G. Cook said that his experience of cortisone in the treatment of œdematous conditions of the macula had not been very encouraging although improvement had been obtained in some cases after a time. It was difficult to assess how much of that improvement would have occurred in the natural course of events, probably accelerated by the hospitalization of the patient. His own belief was that this problem would only be solved by extensive and prolonged investigation. His feeling about cortisone treatment of the condition could be summarized by saying that if he had the condition himself, for want of a better remedy he would try cortisone, but he would not be very optimistic and would therefore not be too cast down if no improvement occurred.

Mr. Hobbs, in reply to the President's question, said that, since general complications were not unknown with this hormone treatment he thought it advisable to hospitalize the patient at least for preliminary observation.

He agreed with Mr. Cook that this was not a simple form of treatment to apply.

Precancerous Melanosis

By C. H. Greer, M.B.

The first writer to use the term precancerous melanosis appears to have been Dubreuilh who in 1912 introduced the designation as an improvement on lentigo maligna which he had employed for the same lesion in previous publications (1894). Twenty-one years earlier, however, Jonathan Hutchinson (1891) had drawn attention to the development of epithelial cancer in senile freckles and areas of dermal melanotic staining in adults and his description of these cases constitutes one of the earliest records of precancerous melanosis.

During the last sixty years a small but constant stream of reports has appeared, especially in the French literature, of conjunctival lesions which may now be reasonably identified as malignant melanomata originating in areas of precancerous melanosis. The authors of these reports have employed a wide variety of terms including melanotic sarcoma, melanotic carcinoma, nævocarcinoma, tache mélanique and lentigo maligna. Descriptions of the conjunctival lesion in its precancerous phase are rare but that of Walker (1928) in the *Proceedings* of this Society under the title of "Melanosis of the Lid and Conjunctiva" appears to be a genuine case although no histological examination had been made.

In 1943, Reese somewhat clarified the position in a paper on precancerous and cancerous melanosis of the conjunctiva and skin. He defined cancerous melanosis as a malignant melanoma originating from a pre-existing precancerous lesion and, in a review of the literature, identified 42 definite or probable cases of this condition. On the evidence of the cases in the literature and of his own experience, he believes that cancerous melanosis is by far the commonest type of malignant melanotic growth of the conjunctiva, and that malignant change in a congenital pigmented nævus is rare.

Our experience at the Institute of Ophthalmology is somewhat different. Of 153 pigmented lesions of the conjunctiva, limbus, caruncle and plica semilunaris examined histologically since 1948, 118 (77%) were nævi; 30 (20%) were malignant melanomata; 5 (3%) were precancerous melanoses.

Of the 30 malignant melanomata, 3 showed surviving islands of small, typical, quiescent nævus cells, suggesting a nævus origin and 9 were malignant melanomata, developing in areas of precancerous melanosis of which there was histological evidence in the epithelium at the perimeter of the malignant focus. In the remaining 18 cases there was no *histological* indication of the mode of origin of the malignant growth, which may therefore have developed from a nævus, from a precancerous melanosis or, *de novo*, without a pre-existing lesion. In addition, among the 118 nævi, there were 10 in which increasing size, deepening pigmentation, cellular pleomorphism and histological evidence of commencing submucosal penetration, suggested early malignant change. These figures show that precancerous melanosis of the conjunctiva is a rare condition, and that in the majority of cases excision is not done until the cancerous phase has supervened. In addition, they support the view that malignant change in a conjunctival nævus probably occurs more often than Reese has suggested.

Clinical Features

The lesion commences as a flat pigmented macule and spreads gradually, remaining flat and extending laterally, until eventually the whole bulbar and palpebral conjunctiva, caruncle and adjacent skin of the lids may be involved in a flat finely granular pigmentation. We have observed that, in its early stages, the lesion may reproduce with extraordinary exactitude the appearance of candle wax spread thinly upon the conjunctival surface. Occasionally the precancerous change synchronously develops over the greater part of the conjunctiva, a fact which can be appreciated clinically only by the minutest scrutiny. While the common tendency is for the lesion to spread and enlarge progressively, spontaneous regression has been noted. In one of Reese's cases the lesion became clinically extinct without treatment but later reappeared.

The precancerous phase commonly lasts for 5–10 years but may be shorter or much longer. According to Reese malignancy almost invariably supervenes. One or more malignant foci develop, either simultaneously or successively and although these may become elevated to form obvious tumours they more often remain almost flat and may, indeed, metastasize and kill the patient without becoming appreciably raised above the surrounding epithelial surface. Enlargement, deepening pigmentation and inflammation in the precancerous area have been the common signs of malignant change but these may well escape detection unless the patient is under close surveillance.

Histogenesis

The earliest changes, which closely simulate junctional change in a pigmented nævus, occur in basal cells of the epithelium over a wide area (Fig. 1).

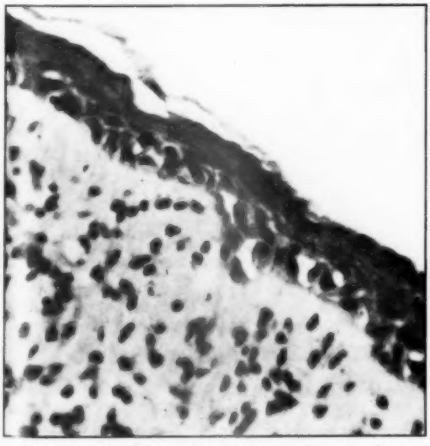

Fig. 1.—Early junctional change showing basal-cell multiplication, hyperpigmentation and vacuolation. × 320.

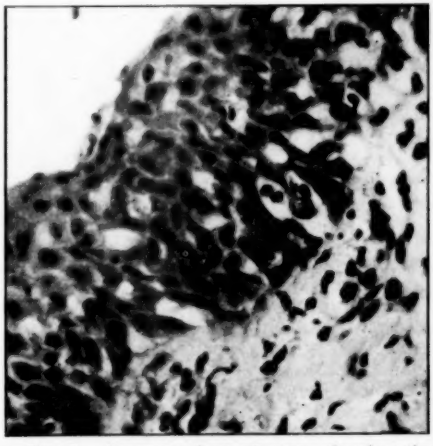

Fig. 2.—A more advanced stage showing the addition of several layers of proliferating cells to the deep surface of the epithelium. × 320.

These cells multiply in number, increase in size and become pigmented and separated from one another by clear spaces. The cells now show large pale nuclei and abundant cytoplasm which may be clear, contain fine pigment granules, vacuoles or droplets, or exhibit a fine cytoplasmic network

FIG. 3.—The proliferating cells segregated to form intra-epithelial pigmented nests. × 320.

FIG. 4.—Isolated pigmented cells working towards the surface. × 320.

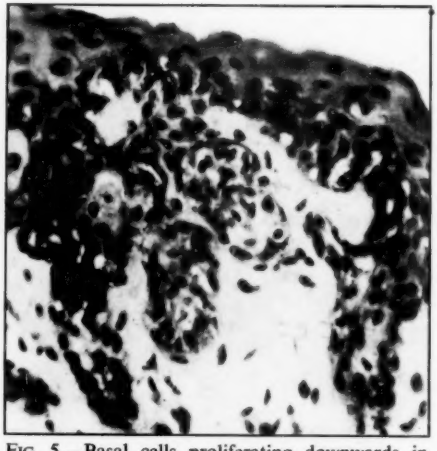

FIG. 5.—Basal cells proliferating downwards in solid buds and branching strands. × 320.

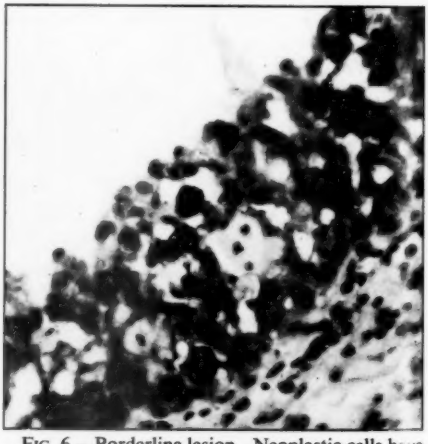

FIG. 6.—Borderline lesion. Neoplastic cells have largely replaced the epithelium without, however, invading the submucosa. × 320.

similar to that seen in foam cells. Contiguous cells fuse to produce spaces containing degenerate nuclear fragments (Fig. 2).

The cells proliferate *intra-epithelially* adding several layers to the deep surface of the epithelium or segregate to form *intra-epithelial* nests which contrast sharply with the normal mucosa in which they lie. It is these pigmented nests which impart the characteristic granularity to the surface of the lesion (Fig. 3).

Isolated clear or pigmented cells may also be seen being worked through the epithelium towards the surface (Fig. 4).

As the lesion develops the proliferating cells push downwards either in strands or solid buds and the submucosa is invaded by chronic inflammatory cells among which macrophages loaded with coarse pigment granules may be seen (Fig. 5).

Histologically the onset of malignancy is indicated by invasion of the submucosa by large, globular, clear or finely pigmented malignant cells from the overlying mucosa where they are present in large numbers throughout all its layers. Nuclear anaplasia and vacuolation and mitotic figures are additional indications, the latter being particularly significant as they are rarely, if ever, seen in the precancerous phase. Submucosal small round-cell infiltration is usually evident (Fig. 6).

Malignant melanoma supervening upon precancerous melanosis has been termed by Reese cancerous melanosis. This seems an unnecessary elaboration of an already confused nomenclature, for cancerous melanosis is clinically and histologically a superficial malignant melanoma and is identical with the superficial melanocarcinoma of Allen and Spitz (1953).

Discussion

Reese defined precancerous melanosis as an acquired neoplastic change occurring in the conjunctiva of middle-aged and elderly persons, and noted that it also occurred in the skin. He distinguished sharply between precancerous melanosis and the pigmented junctional nævus on the grounds that the nævus is a congenital, circumscribed, and elevated lesion, which rarely becomes malignant and is radio-resistant; while precancerous melanosis, on the other hand, is acquired in adult life, is flat and diffuse, inevitably becomes malignant and is radio-sensitive in its early stages. These contentions appear to be based on a very small series of cases—17 in all, of which 5 were in the precancerous and 12 in the cancerous phase. Our experience with pigmented lesions of the conjunctiva leads us to suspect that malignant melanomata not infrequently originate in pre-existing nævi. In addition, the view that precancerous melanosis eventually becomes malignant in every case does not seem to have been satisfactorily proved. Further clinico-pathological observations seem desirable to illuminate this point in particular.

Becker (1954), who is one of the few writers who makes any direct reference to conjunctival precancerous melanosis, believes it to be a form of lentigo maligna, occurring in a mucous surface, but otherwise strictly comparable in morphology and evolution with epidermal lentigo which he regards as melanoma in situ or a premelanomatous condition.

Allen and Spitz (1953) describe an uncommon superficial malignant melanoma (melanocarcinoma), principally in the female external genitalia, which remains flat while spreading centrifugally over wide areas. This is histologically identical with Reese's cancerous melanosis and it seems not unreasonable to suppose that it is sometimes preceded by a precancerous phase. Indeed, it is possible that precancerous lesions occur in other sites such as the oral and nasal cavities, upper respiratory tract and ano-rectal junction, but often remain unrecognized because they are not readily seen and because they produce few symptoms until malignancy supervenes. These authors (1954) also stress the poor prognosis of malignant melanoma in mucous membranes and suggest that the paucity of early symptoms, the misinterpretation of the histological picture of border-line lesions and the difficulties of adequate surgical excision, are among the contributory causes.

For reasons previously mentioned, the introduction of the term cancerous melanosis seems unnecessary, and the question must inevitably arise whether conjunctival precancerous melanosis can be profitably distinguished from the pigmented nævus. We believe that it can and that the two lesions exhibit sufficient differences to merit separate consideration. The reasons for this view may be briefly stated as follows:

(1) Clinically, precancerous melanosis has a characteristic flat diffuse and progressive habit of growth.

(2) Histologically, the junctional proliferation is diffuse and intra-epithelial and the "dropping down" of innocent nævus cells into the submucosa, which is characteristic of nævi, is absent. Indeed, any infiltration into the submucosa of proliferative epithelial cells from a precancerous area must be interpreted as a sign of early malignant change.

(3) Therapeutically, the two conditions differ in that precancerous melanosis is reported to be sensitive to irradiation in its early stages while most nævi are insensitive.

In conclusion it may be said that precancerous melanosis is a proliferation originating in the basal cells of the conjunctival epithelium, analogous to Bowen's intra-epithelial carcinoma or extra-mammary Paget's disease, where that condition can be divorced from any primary malignancy in the underlying apocrine glands. This view receives support from Stout's (1938) observations upon a rare intra-epidermal amelanotic melanoma in the skin characterized by long duration, superficial spread and a histological picture closely simulating Paget's disease.

It would seem that further clinical and pathological observations are necessary before the nature, habits and relationships of precancerous melanosis can be regarded as finally settled.

I wish to express my indebtedness to Dr. N. Ashton and Dr. H. Haber for their advice and to Dr. P. Hansell for the photomicrographs.

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The President said that he had records of 4 cases which bore upon this subject, dating from 1923, 1929, 1935 and 1937. The first, Annie W., was reported at the Ophthalmological Society's Congress in 1951, having been mentioned briefly in the *Proceedings* (Neame, 1929, 1951).

In 1917 the late Mr. Creswell of Cardiff had removed a small growth from the surface of the right eye. In 1919 a recurrence was removed at Moorfields Hospital and a radium plaque was applied to the site. On November 24, 1923, an area of conjunctiva stippled with small discrete pigment spots was removed from the lower ocular conjunctiva, as well as two small projecting growths, by Mr. P. G. Doyne. Dr. Norman Ashton had kindly examined these sections later and reported "a tumour of undoubted malignancy. The cells appear to be rapidly dividing and mitotic figures are numerous. One can see the remnants from the pre-existing nævus from which this arose." On December 15, 1927, Mr. Doyne had excised the eye on account of multiple nodules of recurrent growth at several parts all around the cornea, lying on the sclera. In addition there was a strip of ocular conjunctiva separated by a narrow band of normal-looking conjunctiva below the cornea, once more presenting brown pigment patches. The pathological report on sections was ". . . epibulbar growth part like spindle-celled sarcoma, part alveolar. Slight superficial scleral invasion." This seemed to have settled the matter, for in reply by post to his inquiries in 1929, 1946, 1950 and 1953, Mrs. W. stated that she had had no further trouble, and in 1950 her doctor examined the socket and said it was "splendid".

The second case was reported by the late Mr. J. F. Cunningham (1929). The first examination had been made at the Central London Ophthalmic Hospital on February 21, 1929, and the condition at that time was "a fleshy elevation which moves with the conjunctiva". In addition "pigment is seen to be passing along the conjunctival vessels from the outer side and is encroaching on the cornea". The man's age was 49. It was proposed to remove the fleshy mass and examine it histologically. He had been unable to trace the in-patient notes on this case.

The third case came within the same category by reason of the presence of a very dark brown pigmented spot, about 2 mm. in length, just within the limbus and adjacent to the lower nasal angle of a conjunctival growth. It was a brown pigmented vascular mass with abundant blood vessels converging upon it to the temporal side of the left eye, in a man aged 56. The superficial layers of the cornea were shaved off with a Bier's knife to include the pigmented spot, and incisions carried into the conjunctiva so as to remove the growth in one piece with a margin of apparently healthy conjunctiva. The histological report was "superficial structure suggestive of a mole. No evidence of deep extension". A large, deeply pigmented mass had been noted on the temporal side fixed to the sclera four years later. Exenteration was advised but postal information revealed that the patient died six months after the last visit, at the Miller Hospital, Greenwich, from pneumonia. Post-mortem examination disclosed no evidence of metastatic growth.

The fourth case did not display melanosis except in the presence of fine pepper-like pigmentation on the corneal side of the small growth. The photograph showed the marked vascularization suggestive of early malignancy. This was in a woman aged 60.

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Dr. Norman Ashton said that as yet no one had had sufficient experience of cases in which the clinical and pathological pictures were correlated to come to any final conclusions about the true nature and prognosis of the disease. A useful analogy could be made between precancerous melanosis and Bowen's intra-epithelial carcinoma. The characteristic feature in both cases was the limitation of the tumour cells within the epithelium for long periods, but once frank malignancy developed with dermal invasion, there appeared to be little histological difference between the ordinary type of melanocarcinoma on the one hand and epidermoid carcinoma on the other. Thus precancerous melanosis would appear to be merely a variety of melanoma and one should be cautious of accepting the view that it had a distinct histogenesis: it had been suggested, for instance, that precancerous melanosis arose from basal cells whereas nævi were neuro-ectodermal in origin. He would not have thought that there was likely to be any difference in radio-sensitivity between the two types of melanomata in their malignant phases. Careful follow-up of cases was urgently required and it would be some years before much of value could be added to Dr. Greer's account.

Mr. E. F. King enquired whether this change in the conjunctival epithelium was also seen in the corneal epithelium. He had treated a patient for some time for superficial punctate keratitis which was extremely resistant. Later this patient developed a small fleshy nodule at the limbus which was excised and which examination showed was a malignant melanoma which had not been suspected. The eye was removed and pathological examination showed extensive changes of precancerous melanosis in the epithelium of the cornea and conjunctiva on both sides of the limbus.

Dr. Greer, in reply to Mr. King, said that, in his limited experience of this rare condition, corneal involvement was not uncommon if the lesion was near the limbus. In one case which he had seen, the histological picture suggested that the corneal epithelium was actually undergoing precancerous proliferation. This was impossible to prove conclusively but it certainly appeared to be the case.

Section of Physical Medicine

President—Doris Baker, M.D., F.R.C.P.

[*March* 10, 1954]

DISCUSSION: THE SOCIAL ADJUSTMENT OF THE PHYSICALLY HANDICAPPED

Dr. F. S. Cooksey: During the past decade Parliament has made extensive provision for the security and welfare of the people and particular attention has been paid to the needs of the disabled. If account is taken of permissive as well as mandatory powers it is fair to say that, as far as legislation is concerned, provision for the care of the handicapped is comprehensive and well-nigh complete. Unfortunately, in many respects, executive action lags far behind permissive legislation and there is widespread ignorance amongst the public and the professions concerned of what is already available and of what is still needed. One aspect I wish to stress concerns the cost; because, whether we like it or not, we are now in the position of having to justify expenditure on new developments in Medicine and the allied services. I believe it is possible to show that much that is needed for the welfare of the individual will aid the national economy and that many of the facilities we require are already available if we look for them.

Our first aim is to help disabled patients to become independent and self-supporting members of the community and when we succeed the end usually justifies the cost. However, a proportion of patients are too severely disabled for industrial employment, even under sheltered conditions, or perhaps, like housewives and the elderly, they would not be employed in any event. In such cases we may be asked if we can justify expenditure on medical rehabilitation and welfare services. Often an affirmative answer is to be found by looking beyond the disability to the social problems of the individual, his family and the nation.

For instance it needs about one fit person to look after every two disabled people in chronic institutions and each severely handicapped individual at home may prevent another member of the family from working. Most families are prepared to look after a severely disabled relative at night, but if he or she cannot be left unattended by day the choice may lie between a bed in an institution or keeping a daughter, if one is available, home from work. The latter lowers the family income, possibly to a level requiring supplementation by the National Assistance Board, and deprives the nation of a productive worker. Three common examples can be used to illustrate this matter. Firstly, the wage earner of a family may be permanently disabled and unable to earn his living. If he is able to look after himself at home, and possibly do some of the housework, his wife can go out to work thus restoring the family income and giving the nation a fit worker in place of a disabled one. Secondly, when the housewife is disabled a fit woman in the form of a home help or relative may be diverted from a factory to help or replace the housewife and the cost falls heavily on the family or on the local rates in necessitous cases. Thirdly, parents may look after a crippled son or daughter for many years without help, but when the parents die there is seldom any alternative to a chronic institution unless the cripple has been taught to live in the community and to be as independent as possible of the help of other people whilst still young and adaptable.

Clearly then everything that can be done, within reasonable limits, to help the disabled to be independent of the help of others in the personal activities of daily living and to support themselves in whole or in part is a positive gain to the community. It is with this in mind that we should consider what can be done to help the social adjustment of handicapped patients during and at the conclusion of the medical treatment of disabling illness.

The Personal Activities of Daily Living

Early ambulation after sickness and injury has been shown to be sound practice on medical grounds. It also helps to accelerate the turnover of hospital beds and this is important in these days when the cost of institutional care is so high. Thus there are good reasons for the modern practice of getting patients out of hospital and back to their homes as soon as possible; but in the case of those who are physically handicapped and need help with feeding, dressing and the toilet it may impose a severe, and even intolerable, burden on the family. In the old days of leisurely convalescence in hospitals, larger families and housewives who seldom went out to work, patients and relatives had time to find the answers to many of these personal problems. To-day the shorter stay in hospital and the empty

homes by day make it imperative to teach disabled patients how to be as independent as possible of the help of other people before they are sent home.

In recent years voluntary organizations have done much by means of exhibitions and publications to show what can be done to help patients to overcome handicaps in the personal activities of daily living. What is still needed is to ensure that skilled instructors and the necessary appliances are readily available as soon as patients need them, whether in hospital or under the care of general practitioners at home. Some people suggest that this service should be provided by voluntary or statutory welfare authorities after medical treatment and rehabilitation have done everything possible to restore function. To my mind, help with these personal activities is one of the first and most important steps in rehabilitation which should be an integral part of medical care and applied at the earliest possible moment. It is true that many patients improve and may only need help for a relatively short time. Even so, it is just as logical to teach a hemiplegic patient how to attend to himself with one hand, whilst waiting to see if the affected arm will recover, as it is to use a weight-bearing calliper during the consolidation of a leg fracture.

In hospital this work should be part of the internal nursing and rehabilitation services. In the home I think the instruction of the patient and the provision of personal aids should be the responsibility of the home nursing service; but any necessary structural alterations such as the provision of ramps, hand rails and special toilet facilities might be done by the welfare authority. All that is necessary in hospital is a room where appliances can be kept and instruction given. It is an advantage if it can be situated in or near an occupational therapy department where special appliances can be made and alterations to clothing carried out.

This work can be done by nurses, physiotherapists, or occupational therapists; but it must be studied and carried out systematically if it is to be effective so that whoever undertakes the task must devote adequate time to it. Much of the work is simple and should be included in the routine training of nurses and physiotherapists. Occupational therapists are best equipped to carry out the more specialized procedures and we must hope they will not fail to develop this opportunity.

Simplicity and common sense are the keynote which a few examples will serve to demonstrate. For instance, a hemiplegic man has difficulty in pulling the sleeve of an overcoat over the jacket sleeve on the affected arm, but a loop on the jacket sleeve, fixed in the spastic hand, prevents the sleeve pulling up and overcomes this difficulty. Similarly there are various ways of making it possible for patients with stiff hips or knees to put socks and shoes on and off. Feeding presents many problems, but there are very few, even in the severely disabled, which cannot be solved by ingenuity and simple appliances. High chairs, raised toilet seats and hand rails for arthritics, ramps and wider doorways for wheel-chair cases, a kitchen within reach and suitably adapted and so on will not only give disabled patients independence but will often make it possible for them to be left alone all day whilst other members of the family are out at work.

In my department occupational therapists and physiotherapists are given equal encouragement to do this work, including home visits. We enjoy excellent liaison with the adjoining Metropolitan County Boroughs and the Welfare Department of the London County Council and we have little difficulty in arranging for any necessary adaptations to be made in the homes of our patients. In appropriate cases physiotherapists make remedial exercises more realistic by relating movements to the personal activities of daily living; whilst the construction of appliances and special furniture for the disabled provides worthwhile work in the occupational therapy department which all patients enjoy doing. Most of us have the necessary facilities to undertake this work without additional accommodation or staff and only trivial extra expenditure on raw materials is required. It is one aspect of rehabilitation which can be carried to a conclusion through our departments.

Resettlement Clinics

We have the ultimate social and industrial resettlement of our patients in mind from the onset of sickness or injury; but it is usually towards the end of treatment and reablement in hospital that we feel the need to bridge the gap between our hospital departments and the various authorities concerned with different aspects of social and industrial resettlement. Medical or surgical treatment and the restoration of physical and mental function is carried out by a single team of doctors, nurses, almoners, physiotherapists, occupational therapists and other medical auxiliaries, all in direct contact with each other and with the patient. This team works for a single authority, the hospital management committee, whose members are, or should be, readily accessible to patients and the team. On the other hand, the personnel in the various agencies concerned with social and industrial resettlement are independent central or local authorities and are seldom in contact with each other or with members of the hospital team except by post or telephone. When we consider the separate, and in some respects overlapping functions in rehabilitation of the Ministry of Labour and National Service, the Ministry of Education, The Ministry of Health, the Local Health Authorities, the Local Welfare Authorities and various voluntary bodies it is not surprising that resettlement is often the slowest and most frustrating stage in the rehabilitation of the sick and injured.

Many of us have felt the need to co-ordinate the industrial resettlement of our patients before passing them over to the various agencies to which I have referred. To this end we have established industrial resettlement clinics in our departments and we have found that, in the more difficult cases, a conference between ourselves, our almoner, the Disablement Resettlement Officer from the Local Employment Exchange, the family doctor when he can find time to attend and the patient concerned is constructive and may save much waste of time and effort because a written medical recommendation so often provides inadequate guidance for the Disablement Resettlement Officer. In our work it is also helpful to hear the assessment of the patients by the physiotherapists and occupational therapists who have been treating them and I am sure that attendance at the clinics adds greatly to the interest of these medical auxiliaries. Our colleagues in other branches of Medicine, notably psychiatry, tuberculosis and orthopædics, have also been establishing resettlement clinics for their own cases and have found them equally valuable. There are now close on 100 resettlement clinics throughout the country and I think we are on the verge of general recognition that at least one resettlement clinic should be established in every major hospital.

So far, most of the resettlement clinics have been concerned with the problems of industrial resettlement. In my department for the past two years we have felt the need to establish similar clinics to deal with the more difficult cases of social resettlement. By social resettlement I refer to the adjustment of the home to accommodate severely disabled persons, the training of the disabled housewife and the adaptation of her kitchen and other domestic appliances, the provision of productive or pastime occupations for the home-bound and transport to social activities for the chronic sick and infirm old people.

During the past year, with the co-operation of the Chief Medical Officer and the Chief Welfare Officer of the London County Council, we have been experimenting with a social resettlement clinic. This clinic is attended by the same hospital team but the D.R.O. is replaced by the senior district health visitor and the senior district welfare officer, and is proving just as valuable to ourselves and to our patients in dealing with social conditions as the other clinics assist in solving industrial problems. Most of the cases seem to involve the welfare officer and I believe the medical guidance and other information we are able to provide about the patient is proving just as helpful to the welfare officer as to the D.R.O. Incidentally, both the D.R.O. and welfare officer seem to find it advantageous to be able to bring their problem cases to us for assessment and guidance so these clinics cater for two-way traffic. As far as the health visitor is concerned, it is an advantage to have her present for an occasional case but it seems to us that her role is more related to the earlier stages of convalescence in the home. That is to say, she fits in better with the reablement team and thus liaison with her should be established much earlier in rehabilitation than with the welfare officer.

We hold two industrial and two social resettlement clinics a month, each of two hours' duration. In effect, this means a weekly clinic at which an average of two new and four old cases are considered and this appears to be adequate for the requirements of a large general hospital. Needless to say, the almoners deal with routine cases direct with the D.R.O.s, health visitors, and welfare officers on the recommendation of the consultant concerned. Only the more difficult or interesting cases are brought to the resettlement clinics and these represent between 5 and 10% of all industrial and social problems dealt with by the almoner's department. I find these resettlement clinics fascinating and rewarding and I believe the same applies to the other people who attend. This is one of the most effective ways of integrating the various services concerned with the social adjustment of our physically handicapped patient, but I would emphasize that it is no good waiting for cases to accumulate before convening a clinic. If a regular time is established cases will be referred; but the occasional clinic will peter out for lack of work.

Day Centres

Some severely disabled people are too handicapped to work under industrial conditions even in sheltered workshops. Many of these patients live alone or are lonely by day when other members of the family are out at work. Homework provides occupation but it does not reduce loneliness or relieve the family of finding someone to cook and care for a disabled relative. In our experience there is a real need for day centres in which these patients can work to the best of their ability and feel, as far as their disability allows, that they are still active members of the community. Such centres should help to reduce the need for institutional beds for the chronic sick by making it easier for relatives to keep them at home. A further advantage would be that cripples living alone, or left alone by the death of relatives, would have the opportunity of making friends and arranging to live together in the community instead of drifting into institutions. It is unlikely that the amount of productive work these patients could do would enable them to earn more than the £1 per week which is permitted without interfering with disability allowances. A high proportion would need transport from their homes to the centres, but some patients, who are too disabled for industrial employment, would be able to walk or use public transport. As far as possible, day centres should be run by the disabled people themselves with the minimum of staff in order to keep the cost as low as possible. As to the humanitarian value of such centres, there can be little doubt. Whether they can be afforded depends upon proving that they can be run for less cost than leaving severely disabled

people as a charge on the National Assistance Board at home or on the Local Authorities in institutions. The need for day centres can be illustrated by the example of a young woman of 36, severely crippled by rheumatoid arthritis since the age of 18. For eighteen years she sat by the window all day after being dressed and fed by her widowed mother who is now 68 and cannot be expected to last indefinitely. When she came into our care during an intercurrent illness we found that her arthritis had burnt out and, like other quiescent cases, she has improved with remedial exercises. She has been taught to cook and fend for herself, including going out alone to do the shopping. She now attends that section of my department which is really an experimental day centre and does a reasonable amount of productive work of a marketable standard. At one time there seemed to be no alternative to a bed in a chronic institution for this girl when her mother dies. Now I believe she will be able to look after herself in the community but she needs a day centre in which to make friends and to be able to work within the community rather than to live a lonely existence on the fringe.

Dr. E. Stanley Evans: During the last decade the outlook for the severely disabled has improved materially, as the result of voluntary effort, and of the enlightened legislation incorporated in the Education Act, the Disabled Persons' Employment Act, the National Health (Service) Act, and the National Assistance Act. I shall summarize briefly some of the statutory provisions now available.

Under the National Health (Service) Act arrangements are available for the purpose of prevention of illness, care of persons suffering from illness, or after-care of such persons. The National Assistance Act, Section 29, gives power to local Authorities under an approved scheme to make arrangements for promoting the welfare of persons who are substantially and permanently handicapped by illness, injury or congenital deformity. They may give such persons instruction in their own homes or elsewhere in methods of overcoming the effects of their disabilities, they may provide suitable work in their own homes or elsewhere, and they may help such persons in disposing of the produce of their work.

These Acts provide for:

(1) Supply of appliances and their maintenance.
(2) Well-being of those temporarily or permanently disabled.
(3) Home care of the sick.

The Disabled Persons' Employment Act deals with those who are substantially handicapped and can be gainfully employed. It provides for the maintenance of a register of disabled persons suitable for employment, and ensures that employers of more than 25 persons must employ a quota of at least 3% of such disabled persons. It embodies provision for industrial rehabilitation units, training at Government or at other centres or in industry, and sanctions factory, sheltered or home employment.

There are many gaps in legislation, for, generally, the provisions are permissive, and not obligatory, and the work of many voluntary associations in partly filling these gaps cannot be praised too highly. I propose to deal with one aspect only of the many problems involved in the social adjustment of the physically handicapped, namely with the vocational training of the severely disabled.

Vocational Training Colleges for disabled lads have done magnificent work in this country for forty years or more. Generally, courses of training in the traditional highly skilled crafts such as surgical boot and splint making, tailoring, cabinet making, etc., thought to be suitable for the disabled, have been provided—much in the same way as hospital schools in the past concentrated on handicrafts. Many patients, after months or years in an orthopædic hospital, take exception to the suggestion that they should embark on a course of three years' training in a residential college, necessary for highly skilled trades. And this period is certainly not acceptable to older men who are often married and with families.

Towards the end of the First World War, Robert Jones established curative workshops, where disabled men were occupied with jobs, and workshop activities, as an integral part of treatment. Robert Jones demonstrated the spirit and comprehensive nature of rehabilitation, and it was unfortunate after the First World War that, although treatment for the civilian continued on well-established and progressive lines, the practice of the curative workshop was largely ignored.

It was in this spirit and on this basis that Queen Elizabeth Training College at Leatherhead and St. Loyes at Exeter, and those in Durham and Nottingham were established, and more and more attention was focused on the possibility of fitting into industry individuals handicapped by physical disability by means of occupations other than the traditional crafts. These had the advantage of shorter training and a more elastic qualification at the end of it. It is felt that the disabled should make full use of their mental ability and educational background; but also of the mechanical aids provided by machinery in this industrial age.

In training the disabled vocationally no hard and fast rules can be laid down so far as the various lesions are concerned, for, as with the able-bodied, there are many factors to consider quite apart from the disability, and each presents an individual problem to be judged on its own merits. There are two main groups:

(1) Those disabled in childhood who have never worked and who require training.

(2) Those disabled by accident or disease during the course of employment, who may be able to return to their former work, or to some allied or modified occupation, or who may need to be trained for some entirely different employment.

For all, the basic and essential is that they should have had early and expert treatment resulting in the minimum of disability and the optimum physical and mental recovery. The better the treatment and reconditioning the less the need for re-education and vocational training. Nevertheless, however effective may be the treatment, there will always be many for whom specialized training must be provided and it is with this group I wish to deal. They include:

(1) Those with severe residual disabilities, which may even improve.

(2) Those with chronic, recurrent and progressive disabilities.

Successful training for a specific job depends on:

(*a*) Satisfactory educational standard.

(*b*) Mentality, inclination, keenness and determination.

(*c*) Physical ability.

(*a*) The educational standard must be raised to the level necessary for the job.

(*b*) The desire on the part of the individual to do well and succeed can be fostered by dynamic rehabilitation and by welfare activities and community life in the Training College. Some trainees who are difficult in every way on admission often settle down and become keen, determined and successful workers.

(*c*) In the past, too much attention has been focused on anatomical deformities, imperfections and disabilities, rather than on functional ability. It is important to ascertain what the individual is capable of doing in spite of his disability, rather than on what he is unable to do because of it. Functional analysis must be married to job analysis and job selection. There are many jobs in industry performed by the able-bodied that are far easier than those done by the disabled surgical splint and boot makers, and industrial processes can be broken down into operations that can readily be performed even by the very seriously handicapped. If, for example, an industrial operation can be carried out with one hand, then the one-armed individual is fully competent to undertake such employment, and a chair-bound disabled man may have 100% ability to perform a job requiring only the use of his hands. In general terms it can be stated that a severely handicapped individual can be trained for suitable employment far more readily than he can be to look after himself, for a man with no hands can be trained satisfactorily and obtain work relatively easily, but will have tremendous difficulty in bathing, shaving, dressing and looking after himself generally and in indoor and outdoor recreations.

Physical ability to be trained for and perform a particular job may be governed by several factors, and it must be remembered there are still many admitted to training colleges who have been treated too late and indifferently. They may need: (*a*) further physiotherapy and physical reconditioning, but as in the curative workshops many will improve amazingly while being trained in the job. As one trainee wrote: "I've got more use in my arm after seven weeks' work at the College, than in seven months' sticking to massage and exercises before."

(*b*) Others will need satisfactory appliances, e.g. a knee-jointed caliper, a simple trough splint for the flail elbow, or employment aids or gadgets for upper limb prostheses to enable them to do the job. The provision of zip fasteners for shoes and trousers and of gadgets for pulling on socks will help the arthritics or those with no hands.

(*c*) Orthopædic revision and operative treatment may be necessary, e.g. arthrodesis for the flail shoulder with good scapular movement and power; arthrodesis of the wrist or tendon transference for the flail wrist, or in spastic hemiplegia; operations for opposition of the thumb; sympathetic ganglionectomy for the chair case with cold blue limbs and chilblains; arthroplasty of the hips, and osteotomy of the spine by the expert for ankylosing spondylitis. All such orthopædic treatment must be carried out with a full knowledge of the specific job to be undertaken and of the physical requirements necessary.

(*d*) Industrial adaptations and interest and consideration by employers and fellow workers may make all the difference to success, e.g. a job on the ground floor with a ramp to the shop, alterations to the height of the bench or stool, simple adaptations to plant and machinery such as a longer or cranked lever so that machinery and mechanization can be used to the full as a substitute for physical deficiency. With co-operation, goodwill and determination on the part of the employer and the disabled person it is amazing what can be achieved in fitting the severely disabled man or woman into organized industry, and the work of the Austin and Vauxhall motors in Birmingham and Luton has blazed the trail in this respect.

(*e*) Physical ability to perform a job may be satisfactorily achieved, and yet the individual may find it impossible to secure and retain employment unless other difficulties are overcome. Ground floor accommodation in a bungalow or hostel may be necessary, assistance with bathing, dressing, shaving, may be required and the provision of transport to and from work may be essential.

At Queen Elizabeth Training College, and I deal with this only because I have been associated with it closely for twenty years, over 3,000 men and women have been trained, including:

900 suffering from the effects of poliomyelitis, cerebral palsy, paraplegia, &c.,

300 with quiescent tuberculous lesions,
300 with lower limb amputations,
and perhaps more gratifying than all,
over 300 one-armed men and 16 with no hands.

The author then showed some illustrations showing some of the problems dealt with at the College.

Conclusion.—(1) In dealing with the severely disabled, everything possible must be done from the orthopædic and remedial aspects to enhance physical ability. Preparatory training schemes in long-stay hospitals are invaluable in preparing the patient for his post-hospital career.

(2) Given an adequate education, mental aptitude, inclination and determination, the results of training are often surprisingly good.

(3) For lower limb disabilities and the chair case, training and placement are relatively easy, but locomotion and personal care may prove a stumbling block.

(4) Loss of one hand, or both, greatly limits the possibility of doing a worth-while job, but with suitable employment aids (and Roehampton has done excellent work in this connexion) gardening, book-keeping, machine drawing, spray painting and arc welding at least can be considered.

(5) Each disabled person must be up-graded to the limit of his potential industrial capacity, and it is a *sine qua non* that the only satisfactory conclusion to training is placement in the selected job and the ability to retain it. It follows that the courses of training provided must constantly be reviewed so that trainees may be trained and placed readily in jobs where there are openings.

(6) Further consideration must be given to disabled home workers. More sheltered workshops and hostels are required for those handicapped so severely that they cannot be absorbed into industry.

To quote Carlyle:

"Work is the grand cure of all the maladies and miseries that ever beset mankind."

If this be true for the able bodied, how much more so is it for the severely disabled.

In conclusion I would stress that I have dealt with one aspect only, and perhaps not the most important, of the problems involved in the social adjustment of the physically handicapped. May I enumerate some of the needs for the future.

(1) Prevention and adequate early, expert treatment.
(2) Dynamic rehabilitation throughout, to minimize and overcome disability.
(3) Closure of the gap between hospital, training and employment.
(4) More facilities for secondary, grammar school and University education of the physically handicapped.
(5) An enlightened psychological approach to the problem of disability, on the part of employers, the public and the disabled themselves.
(6) Less segregation of the disabled and groups of disabled in clubs and societies of their own, and full social adjustment within the community.
(7) And lastly, closer co-ordination between doctors, therapists, and social workers, and Government departments, local Authorities, and voluntary bodies dealing with the physically handicapped.

Group Capt. C. J. S. O'Malley: My task is to focus our attention on some aspects of the social adjustment of the disabled. Firstly their adjustment to work, and secondly, their attitude to play. Both are equally important to the disabled person. Our success in these two spheres is a measure of the total adaptation of the patient to life.

Let us in the first place deal with the problems of work: we should attempt to analyse why a disabled person is not working. The reasons may be divided into:

(1) *Physical*—full restoration of function may not have been obtained and the patient is not using to the maximum the potentialities of what he has got left. Many cases of anterior poliomyelitis have wasted, atonic normal muscles which could be built up by an appropriate regime. I do not have a lift at Garston Manor Rehabilitation Centre. Cases of anterior poliomyelitis arrive anything from four months to two years after their initial attack. Stair climbing is a social exercise; in the first week they may take as much as forty minutes to achieve this task; within a few days these stairs are climbed in five to seven minutes. The medical aspects of the stable diseases, such as anterior poliomyelitis, paraplegia, &c., are relatively simple problems from a physical point of view. However, the problem of the unstable diseases, rheumatoid arthritis, disseminated sclerosis and tuberculosis present many more difficulties. Remissions and relapses of pain and the life history of the disease have to be considered. In the stable diseases the physical problem can be overcome by making certain that what has been left to the patient compensates what he has lost—over-development of the trunk and upper limbs in the case of paraplegia allows the patient to live a relatively normal life.

(2) *Psychological*—the academic psychologists were interested in "How we do what we do". From a medical view-point, particularly in regard to the problems of the disabled, we must examine the patient's motivation, "Why we do what we do". There are many psychological causes of maladjustment of the disabled person, ranging from a bad reaction to his disability, resulting in the

patient's gradual lapse into his dependence, to aggressive hostility to the world in general and the medical profession in particular.

Assessment of the patient's motivation must in the final analysis be the answer to our problem. Is he escaping from a work situation that was intolerable before the onset of his disability?

Does financial gain motivate his whole attitude? In cases of compensation in Common Law, I have never known a man completely to recover full and efficient function if he is in danger of losing money. This particularly applies to injuries to the vertebral column and the spinal musculature. The amputee can go to court and show the world his disability. The man with an injury to his spinal column has little or nothing to show in court.

Does his injury allow the patient to escape from a marital and social environment to which he is antipathetic? Until we have studied the patient's motivations, we cannot hope to understand the patient's reactions to his disability, his attitude towards his work, his home and his associates.

(3) *Sociological*—under this heading we classify the problems of housing, clothing, transport, education and the various financial problems which have been brought into high light by the advent of the Welfare State. A disabled man with a large family may not be able to earn a wage greater than the total sum he receives from the Welfare State for doing nothing: Sickness Benefit, Industrial Injuries Pension, Family Allowances, &c.

(4) *Resettlement*—before a man can be resettled in appropriate work, an attempt must be made to assess his capacity to work, and to equate this assessment with the local work situation.

Many attempts have been made in the past

(1) To analyse the man's physical and intellectual capacity.

(2) To analyse the job—how much standing, walking and movements of the upper limbs are required and for how long. Hanman in America and Sweden has suggested a scientific method of matching the man to the job. But he has failed in his method to take much account of the patient's motivation. His whole system fails when the patient says "I won't". In my opinion there is no better method of assessing a man's willingness and ability to work than making him work under skilled supervision in a remedial workshop. In this workshop—

(1) Restoration of function may be completed.

(2) Restoration of confidence to go back to his original job may be completed by a practical demonstration of his abilities.

(3) Assessment of the man's work capacity may be initiated.

The Aims of Rehabilitation

If I were asked where medical rehabilitation finished and industrial rehabilitation began I would answer that they are one and the same continuous process. The aims of rehabilitation as defined by the Industrial Rehabilitation Committee of the Ministry of Labour are as follows:

(1) The restoration and maintenance of function—both physical and psychological—by means of work, remedial exercises, and other activities carried out under the supervision of a team of specialists.

(2) The assessment of the patient's capacities, both actual and potential, making use of medical and psychological examination and trials in the unit's workshops and gardens.

(3) The assessment, by the same means, of the patient's inclinations, including his attitude to work, to his disability, and to other people.

(4) The resolution, often in collaboration with other agencies, of any personal problems, including marital troubles, housing, clothing, pension, compensation, and artificial aids.

(5) The giving of advice about the choice of suitable employment or training in each individual case, and the communication of this advice to the applicant's Ministry of Labour's employment exchange office.

One of the problems which the disabled have to face in getting back into life, is the regression to the infancy and childhood way of life in a hospital.

In the authoritarian regime of a hospital ward food is brought to the patients, the whole of their toilet is performed by nurses and they have no independent existence.

This dependence is sometimes encouraged by an over sympathetic nursing staff. There is a very great gap between the authoritative discipline of hospital life and the self-discipline of the outside world.

In a residential rehabilitation centre, an attempt should be made to produce a culture of normal living, i.e. people who live at home and go to work. At home the discipline is that of the group, the family, the community; self-discipline and mutual discipline. At work, the discipline is authoritarian: workers have to be punctual and have to be industrious. If they are not, they lose the opportunity of work and gainful employment.

At Garston Manor, the patients live in a Hostel, where the discipline is permissive: the government of the patients by the patients implemented by a Patients' Committee, which is democratically elected.

At the same time, the patients go to the remedial centre for their working day. Here the discipline is authoritarian—the patients have to be punctual, attend their classes, and work diligently, with a culture of self-discipline and mutual discipline, self-help and mutual help.

As patients progress they will do as much as six hours work therapy in one day. This work-therapy regime is equated as near as possible to the job they have to do in the outside world. Agricultural labourers work in the gardens, carpenters do woodwork, bricklayers and plasterers build houses. Mechanics and engineers work on machines which they will use in their own workshop. This regime is realistic in its approach, and once a man has done six hours a day in the Centre it is not a big step to do eight hours in his normal working environment. The whole culture has the form of a democratic approach to life, but the tempo of this life is guided by what we hope is enlightened medical direction, and is, in the last analysis, a benevolent autocracy, with the accent on "benevolence" producing the greatest good for the greatest number.

The problems of play.—Life has been described as being—8 hours sleep, 8 hours work and 8 hours play, and the importance of play has largely been ignored by the medical profession.

We believe that a proper balance between work and play is important in a rehabilitation centre, and I will not enlarge on the use of games as an aid to recovery, but merely state that they are just as important as work-therapy in the indirect approach to remedial exercises.

However, the social regime at a rehabilitation centre is a vital part of that culture.

Such activities as dances, whist drives, concerts organized by patients, outings to football matches, &c., sports days, rambles, outings on cycles, periodic visits to places of amusement, all allow the patient to return to life, and overcome the apathy and ennui of the isolated disabled person. It allows them to get away from the authoritarian, over-protective atmosphere of a hospital, and become trained in the activities of daily living. The importance of this regime is particularly noticeable in overcoming the emotional block which occurs in almost every young girl who is afflicted with anterior poliomyelitis. We have had many patients, girls with bilateral calipers, who learned to dance at the rehabilitation centre, and become so socially adjusted, that they have attended public dances happily, and without psychological trauma.

Another important aspect of training for daily living is the fact that we have an enlightened London Passenger Transport Garage near the Centre. Due to the understanding of this Garage Management, patients can practise getting on and off buses, which are driven up to the patients, and driven away again at increasingly shorter periods. Thus the patients become used to getting on public transport before they are thrown into the maelstrom of the rush-hour. One of the greatest difficulties we find is overcoming the cult of the wheelchair, which limits many patients' activities, whose physical condition does not warrant this limitation.

Conclusion.—A state that spends large sums of money in medical research to prolong the years of life cannot divorce itself from the responsibility of giving life to those years so prolonged. The disabled have a right to live, to work, to play, to have normal independent lives in normal communities. Segregation and isolation may have advantages in the scientific study of disease and disability, but are the antitheses of normal living. This is a challenge facing the country in general, and the National Health Service in particular.

Section of Comparative Medicine

President—Professor T. J. Bosworth, M.A., B.Sc., M.R.C.V.S.

[*April* 21, 1954]

The Effects of Antibiotics on the Body Functions of Man and Animals

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It is the privilege of an opening speaker to range at will over the broader aspects of a subject, defining its scope and re-stating a good deal of common knowledge about it. He may leave it—at least I hope I may—to those who follow him to add something original and more interesting about its individual aspects. I must confess that my chief interest in antibiotics is in an aspect of their activity which is specifically excluded from our subject, and I do not claim to be an authority on any other.

I need hardly remind you that the ideal chemotherapeutic agent is a drug which has no action on the body whatever. Thousands of antibiotics are known, many of them with high degrees of antimicrobic activity, and the fact that only about nine are in general clinical use is explained by the toxicity of the remainder, i.e. their damaging action on various organs and tissues. This is not to say that even those nine are entirely free from toxicity, and this is the first of five kinds of effect other than specifically antimicrobic, which it is necessary to consider.

Penicillin is the only antibiotic, and indeed the only chemotherapeutic agent of any kind, which is entirely non-toxic. Its administration is not free from risk but reactions to it occur only in sensitized individuals, which is a rather different matter. Of the remainder streptomycin has a peculiar selective action on the VIII nerve, producing either vertigo or deafness or both, chloramphenicol can produce bone marrow aplasia, Aureomycin or terramycin in excessive doses damages the liver, and bacitracin and to a lesser extent polymyxin damage the kidney. It is interesting that antibiotics have now been found and brought into general use which attack all the body tissues most susceptible to attack by drugs of other quite different kinds. I confess I am quite unaware whether such effects have been encountered in veterinary medicine, but I should suppose that in larger animals at least it is rarely feasible to give any drug in sufficient doses or for long enough to produce them.

I should imagine that reactions due to sensitization are also rarely seen in animals, since very extensive use precedes their appearance. The most serious of these, oddly enough, are produced by penicillin, and many fatalities are now on record, death having occurred from what appears to be anaphylactic shock. Such patients have invariably been given the drug before, and it may be presumed that they are sensitized to it in the true sense of having formed a specific antibody. If so, penicillin must function as a haptene, and it is well known that during administration much of the circulating drug is combined with plasma protein. On the other hand, the rapid development of this shock-like state would seem to require rapid absorption, and in fact a majority of these reactions have been caused by slowly absorbed preparations, chiefly of procaine penicillin. The possibility of such reactions has become a powerful argument against indiscriminate use. Sensitization to other antibiotics is possible, although it rarely has such serious effects, and is only likely to prevent administration when the route is parenteral: streptomycin is thus the only other commonly used drug liable to cause serious trouble. A peculiar and very disabling form of streptomycin sensitivity is that seen in nurses who contaminate their hands and faces with the solution when giving injections. Deliberate application to the skin therapeutically is particularly liable to sensitize whether antibiotics or sulphonamides are used. There is now, consequently, a tendency to avoid for this purpose the main antibiotics which are used systemically and to substitute some other with an adequate local effect, although perhaps unsuitable for systemic use. Neomycin, for example, has a similar antibacterial action to that of streptomycin but is distinct from it as a sensitizing agent; it can therefore be applied locally—and has in fact been extensively used in dermatology—without fear of creating difficulties should the patient have subsequently to be given streptomycin by injection.

All the other undesirable effects of antibiotic treatment of which I am aware are due to action on bacteria other than those causing the infection which is being treated. Suppression of the bowel flora, as by Aureomycin or terramycin, will eventually interfere with vitamin synthesis, particularly that of nicotinamide. This can always be remedied by supplying the necessary vitamins. A much more serious consequence, not so easily remedied, is the development of a superinfection, i.e. a new infection resistant to the drug being used. There are four possible explanations of this occurrence.

It was first described years ago in connexion with the use of penicillin: a patient with a pneumococcal pneumonia would do well at first, then relapse, and be found to have sputum full of *H. influenzæ*. The probability is that the second and more resistant organism had been there from the first and was merely unaffected by the treatment. The superinfections we are seeing now are produced either by the newer "broad spectrum" antibiotics or by penicillin and streptomycin used together; the effect of full doses of these drugs, particularly the former, is to suppress most of the normal flora of the mouth, upper air passages and intestinal tract. The consequence of this may be an infection involving any of these areas, and sometimes the bronchi and lungs, due to an antibiotic-resistant *Staph. pyogenes*, or *Candida albicans*, or both. A peculiar form of this infection, only recently recognized, is a very acute staphylococcal enteritis, which may be fatal.

My three remaining explanations refer to these conditions. There is the obvious one that suppression of the normal flora creates a microbic vacuum which any opportunist can fill. It is also likely that the normal balance is partly maintained by antibiosis; several of the commonest normal inhabitants of the alimentary tract are known to form antibiotics themselves. Thirdly there is the possibility that the drug in use directly stimulates resistant species. There is abundant evidence that sub-inhibitory concentrations of various antibacterial substances, including antibiotics, can accelerate bacterial growth. How important this effect is clinically we do not know. It is at least worthy of further attention, and I ventured to suggest some years ago that the alleged stimulation of *Myco. tuberculosis* by penicillin might mean that the use of this drug—for some other indication, of course—in tuberculosis is inadvisable. One possible illustration of this is the reported development of severe tuberculous mastitis after injection of penicillin into the teat canal. Was this due simply to the transfer of tubercle bacilli from other cows, or did penicillin activate a previously latent infection?

Lastly, the one beneficial effect of antibiotics apart from their main use is their growth-promoting effect when antibiotic residues or small amounts of the drugs themselves are added to the diet of young stock. The nature of this effect seems not yet to be fully understood, but two factors, apparently, may contribute. One is the suppression of infection by unrecognized pathogens, the other an alteration in the balance of the intestinal flora favouring the synthesis of some possibly unknown growth factor.

The Growth-promoting Effect of Antibiotics and their Possible Modes of Action

By W. S. Gordon, M.R.C.V.S., Ph.D., and J. H. Taylor, F.R.C.V.S.
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In recent years a new effect of antibiotics on body functions, that of increasing the growth rate of most young rapidly growing animals, has been discovered. This effect was first reported by Moore *et al.*, in 1946, since when it has been widely applied in this country and in the United States, bringing about a considerable increase in livestock production.

The original work was confirmed when Stokstad and Jukes (1950) showed that pure Aureomycin Hydrochloride would increase the rate of growth of the young chick. Similar results were reported in the pig (Jukes *et al.*, 1950) and were amply confirmed by many other workers (reviewed by Braude *et al.*, 1953). In this country extensive pig-feeding trials using Aureomycin and penicillin were organized by the Agricultural Research Council and served to confirm in general the American findings (*A.R.C. Report Series* No. 13, 1953; Gordon and Taylor, 1953). The optimum dose rate is at present being ascertained but it is generally considered to be between 4 and 20 parts per million (p.p.m.) in the food. The chicken may benefit from as little as 2 p.p.m. of penicillin.

A great deal of literature on the subject has appeared since 1950 and it is only possible in this short contribution to mention a few points of special interest. The subject has been comprehensively reviewed by Jukes and Williams (1953) and Stokstad (1954).

There is now overwhelming evidence to show that a wide range of antibiotics when fed in very small quantities will increase the growth rate and efficiency of food conversion of many species, including man. Several workers have shown a marked increase in growth and survival rate of premature infants (Snelling and Johnson, 1952; Robinson, 1952) and Carter (1954) is obtaining a remarkable growth response and reduction in disease level of children fed 75 mg. Aureomycin twice daily.

Of the many hypotheses on the mode of action of antibiotics in stimulating growth, none, so far, provides a complete explanation of many observations which have been made. It can be seen from Table I that we are considering a phenomenon in which the "normal" organism, whether it be mammal, bird, or plant, can benefit from a group of substances whose only common characteristic, as far as we know, is the ability to kill, or depress the growth of certain micro-organisms. There is good evidence to suggest that it is this characteristic of the antibiotics that is responsible for the phenomenon that we are studying. The fundamental study of "germ-free" life at the Lobund Institute clearly shows that the "germ-free" animal derives no benefit from an antibiotic supplement but will grow as fast as a conventional animal receiving such a supplement (Luckey, 1952). Thi

TABLE I.—THE EFFECT OF FEEDING AN ANTIBIOTIC SUPPLEMENT TO A VARIETY OF SPECIES
The Approximate Benefit which May be Derived by the Young Organism

Class	Order	Species	Antibiotic fed	Duration of feeding	% increase in growth rate	% saving in food consumption	Authors
Mammal	Ungulate	Cattle	P	12 weeks	0–10		Knodt and Ross (1953) Kon *et al.* (1953)
			A	8–16 weeks	15–35	10	Murley *et al.* (1952) Jukes and Williams (1953)
		Horse	A	9 months	11	0	Unpublished
		Pig	P A	13–20 weeks	11 13	6 7	*A.R.C. Report Series* No. 13 (1953)
		Sheep	A	16 weeks	9	5	Bridges *et al.* (1953)
	Carnivore	Dog	A	20 weeks	12	5	Arnrich *et al.* (1952)
	Rodent	Mouse	A	10 weeks	11	—	Mirone (1953)
		Rat	P	5 weeks	7	10	Unpublished
			A	5 weeks	15	13	
	Primate	Man	A	1–3 years	65	—	Carter (1954)
Bird	Rasores	Chicken	P and A	6 weeks	8–13	7	Heuser and Norris (1952)
		Turkey	P and A	8 weeks	10–30	10–20	Wilson (1953) Stokstad (1954)
	Natadores	Duck	P and A	6 weeks	0	0	Branion *et al.* 1953
		Goose	P	8 weeks	5	9	Branion and Hill (1952)
			A	8 weeks	8	10	
Fish	Teleostei	Guppy (*Lebistes reticulatus*)	A	6 months	–70	—	Berke *et al.* (1953)
Plant (Dicotyledon)	Cruciferæ	Radish	P	Germination and maturity	154	—	Nickell (1953)
	Polygonaciæ	Sorrel	Terramycin	4 weeks	18	—	

P—Procaine Penicillin. A—Aureomycin Hydrochloride

supports the work of Jukes *et al.* (1952) who showed that the chick embryo, being sterile, would not benefit from an antibiotic supplement. Further, when the antibacterial properties of an antibiotic are removed it no longer appears to possess the ability to stimulate growth (Jukes and Williams, 1953).

Pursuing the hypothesis that the beneficial effects result from the influence of the antibiotics on micro-organisms within the animal, extensive studies on the effect on the flora of the digestive tract have been made (Coates *et al.*, 1951; Sieburth *et al.*, 1951; March and Biely, 1952; Eisenstark and Sanford, 1953) without revealing any consistent change in the flora to which could be attributed the beneficial action of an antibiotic. This, however, may be due to an inability to detect the particular organisms implicated, or to changes in the metabolism of these organisms which would benefit the host, but which might not be detected by a viable count. The difficulties of interpreting apparent changes in gut flora have been described by Reyniers (1952).

There is some evidence that there is a change in the environmental flora associated with the use of antibiotics and it has been shown in this country that chicks reared in a long-established poultry house benefited from an antibiotic supplement, while those reared in a new house did not. The chicks kept in the new house grew as well as the antibiotic-supplemented animals in the old house (Coates *et al.*, 1952). In this connexion it has been suggested that the presence of an antibiotic removes some "latent infection" which normally depresses growth. In support of this hypothesis we have observed during the last two years an increase in the growth rate of control pigs on premises where a succession of antibiotic feeding experiments have been carried out. These results are shown in Fig. 1.

Within the normally accepted dose range the quantity of antibiotic fed is of the order of 0·5 mg./kilo body weight per day. Although this is far below the usual therapeutic level, when administered continuously it appears to control many intestinal pathogens. Becker *et al.* (1952) attributed at least

part of the action in stimulating the growth of pigs to the prophylaxis of disease. Burnside *et al.* (1953) controlled a natural outbreak of dysentery in pigs by feeding 20 p.p.m. of Aureomycin in the food. Several workers have shown a very marked response to antibiotics in the "runt" pig (Catron and Cuff, 1951; Worden and Bunyan, 1952). In trials involving 120 calves we have observed a statistically significant reduction in mortality due to enteritis associated with *Bact. coli*. It seems then that at least one of the effects of such a supplement when fed within the higher dose-range is to control certain bacterial diseases, although the specific protection afforded has not yet been investigated or artificially challenged.

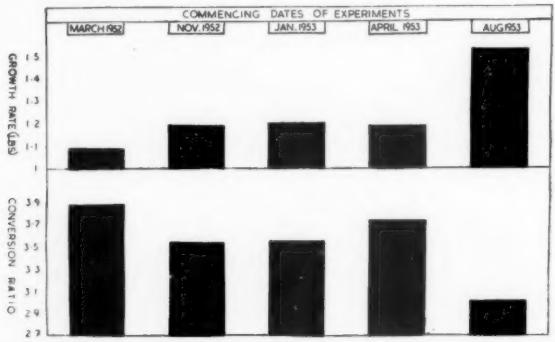

FIG. 1.—Comparison of growth rates and food conversion ratios of control pens in successive antibiotic pig-feeding trials at Compton.

As a preliminary investigation into the possible modes of action, we have examined the distribution of two antibiotics, penicillin and Aureomycin, throughout the length of the digestive tract, the body fluids and tissues of animals receiving varying doses of these supplements. By examining material from several hundreds of pigs and also horses, calves and rats, we have accumulated considerable information which will be fully reported later but which is possibly of interest to mention now.

FOOD (Parts per million)	CONCENTRATION OF ANTIBIOTIC CONTENT OF: STOMACH	SMALL INTESTINE	CAECUM	LARGE INTESTINE	BLOOD SERUM	URINE
PROCAINE PENICILLIN						
4	+ +	+ +	−	−	−	+ +
128	+ +	+ +	−	−	+	+ +
AUREOMYCIN HYDROCHLORIDE						
4	+	+ +	+	+	−	+ +
128	+ +	+ +	+ +	+ +	+ +	+ +

FIG. 2.—Sites of detection of antibiotics in the pig following administration at varying levels in the food (one to three hours after feeding). + = minimal detectable levels. Variation from 0·008 to 0·02 μg./ml. or μg./gramme according to material examined.

Fig. 2 shows that there are differences in the distribution of the two antibiotics, the most marked being the absence of penicillin in the cæcum or large intestine even at the higher dose level whereas Aureomycin is detectable throughout the digestive tract. This might suggest that any effect on the intestinal flora is confined to the organisms in the upper part of the digestive tract. It is also noteworthy that both antibiotics when fed at levels as low as 4 parts per million of the food are not confined to the digestive tract, but are excreted in significant concentrations in the urine. Further evidence of their distribution within the body is furnished by the detection of both antibiotics in the blood serum at the higher dose-rate.

These findings may throw some further light on the possible mode of action of antibiotic supplements, for although there is much support for the theory of an antimicrobial action, it has so far been considered that this action could only take place within the digestive tract, where it was assumed

that the antibiotic was confined. The theory of subclinical disease control is perhaps more acceptable in the light of these findings.

To summarize, we have considered the establishment of a growth response with antibiotics and have shown the wide variety of species in which this phenomenon occurs. We have considered a few of the possible modes of action and have suggested that the depression of sub-clinical disease is a hypothesis worthy of attention. There are, however, many other aspects of the subject which we have been unable to consider in the present paper.

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The Function of Antibiotics in Animal Nutrition

By S. K. Kon, Ph.D., D.Sc., F.R.I.C.

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Work on the use of antibiotics in animal feeding has been going on at the National Institute for Research in Dairying for several years now, having begun shortly after the original announcement of Jukes, Stokstad and collaborators in the United States that antibiotics added to the diet exerted a favourable effect on the growth of pigs and poultry. In our experience pigs could be brought to bacon weight more rapidly when an antibiotic, penicillin or Aureomycin, was added to the diet at the rate of about 12 mg./ton food. The effect was noticeable both with rations containing animal protein, more customary in this country and with rations containing only vegetable protein. It was perhaps more marked with the latter diet and the growth increment was on the whole of the order of 10%.

Our experiments with calves were done with our own calves born on our farms and also with

calves brought from outside. It is well known that calves whose environment is changed are more likely to be unthrifty and suffer from scouring than animals reared where they were born and it is with such calves that we found consistently beneficial effects from the administration of antibiotics in the food, consisting of milk alone at first, later supplemented with hay and concentrates. Procaine penicillin equivalent to 80 mg. penicillin/calf/day or Aurofac 2A supplying 50 mg. Aureomycin/calf/day, increased the growth rate of such calves up to 3 months of age from about 1·1 lb./day for the controls, to 1·3 to 1·4 lb./day for the treated animals. At the same time the incidence of scours was markedly reduced and the general appearance of the calves improved. Healthy calves of our own breeding grew in one trial without antibiotic supplements at rates similar to those of the calves just mentioned given antibiotics, and with them antibiotic treatment produced no obvious effects though in a second trial, when scouring was prevalent, antibiotics did improve growth and reduce the scouring. Under practical conditions calves often suffer from intestinal infections and it is our belief that by and large the use of antibiotics in calf feeding in this country would be beneficial.

Our main work on the dietary use of antibiotics, and one which I should like to stress since it dealt largely with the mode of action of the antibiotics, was with poultry. Chicks have been kept at Shinfield for experimental purposes for some fourteen years now and at an early stage of our antibiotic work we confirmed with them the efficacy of antibiotics with a variety of diets, practical and experimental and with or without animal protein. When some of these results were reported in October 1950 at a meeting of the Biochemical Society, workers at the Glaxo Laboratories Ltd. pointed out that in similar experiments they found no effect of antibiotics. As chicks had not been kept at Glaxo Laboratories before it seemed possible that the difference was due to environmental conditions and joint experiments were done to clear up this point. Day-old chicks from one hatchery were distributed between the Glaxo Laboratories and Shinfield and received in both places chick mash derived from one batch. No effect was obtained at Glaxo Laboratories but the antibiotic (procaine penicillin, 40 mg./kilo diet) was again effective at Shinfield, the birds receiving it growing at the same rate as the birds at Glaxo, whereas the growth of the untreated birds at Shinfield was less. In a further experiment the chicks were similarly distributed and treated but, in addition, they were also kept at Shinfield in a laboratory where chicks had not been before. These birds behaved like the birds at Glaxo in that they did not respond to the antibiotic and without it grew better than the untreated birds in the old premises. It thus became evident that under our conditions the antibiotic was acting not so much by accelerating growth as by removing some depressant effect present in surroundings where chicks had been kept for a long time. Careful search failed to detect in our chicks, responding to antibiotics, any obvious known disease or infection and in fact they were by all customary standards quite normal, the only difference between them and the chicks kept in the new place being in the slightly lower rate of growth. To study the way in which the antibiotic acted on our birds, Perspex isolation boxes were established in each of which two cages of day-old birds could be sealed with enough food to last for twelve days. Drinking water was supplied by a closed cistern and bacteriologically filtered air was circulated through the box. Birds in one cage received the diet alone, those in the other with the antibiotic. Under such conditions the depressant effect which for want of a better term we described as "infection", could be produced by sprinkling on the food the fresh gut contents from "infected" birds but not gut contents of birds kept under conditions where the antibiotic was inactive. Autoclaving of the gut contents prevented the transmission of the "infection".

Although the penicillin increased the weight of chicks it had the opposite effect on the weight of the small intestine and when due allowance was made for the greater size of the treated birds their small intestine was lighter than that of the controls. In all probability this change in weight of the intestine is connected with the state of "infection" of the bird and is not a non-specific effect of penicillin since the antibiotic did not alter the weight of the gut of birds free from the "infection". It is of interest in this connexion that in all their studies of animals kept under sterile conditions and free from any micro-organisms in their gut, Reyniers and his colleagues at Notre Dame University in the United States found that the gut of such animals (chicks and rats) was lighter than that of normal animals carrying the usual microbial gut burden.

Since our observations on the relation of antibiotic activity to environment were published, workers in several laboratories in the United States and in this country reported similar findings. It does seem established that, with chicks at any rate, the growth-promoting effect of antibiotics, or rather the suppression of retardation of growth, is in some way connected with the intestinal population of the animal. We are at present studying the bacterial population of the chick, both "infected" and non-"infected", and the effect on it of antibiotics. As the knowledge of even the normal flora of the chick is very fragmentary much work will have to be done before the mode of action of antibiotics becomes clearer.

Section of the History of Medicine

President—The Right Hon. Lord WEBB-JOHNSON, G.C.V.O., C.B.E., D.S.O., T.D., M.B., F.R.C.S., LL.D.

[*March* 3, 1954]

Dr. John Calthrop Williams, Physician of Nottingham 1801–1856

By P. H. O'DONOVAN, M.D., F.R.C.P.

INTRODUCTION

JOHN CALTHROP WILLIAMS was born on May 30, 1801, in Bridlesmith Gate, Nottingham, within the very shadow of St. Peter's Church, and he lived nearly all his life in houses situated within a few hundred yards of this church. If the years he spent out of Nottingham, mainly for his education, are subtracted, some fifty years were still spent in his own town.

My interest in Dr. Williams was first aroused by seeing the facsimile of a title page of a volume printed in 1832, reproduced in the standard textbook "Heart Disease" by Paul Dudley White, M.D. The importance of this volume can be judged by the fact that it is the only one honoured by having its title page reproduced in the textbook. The author, John Calthrop Williams, is described as "a man of Edinburgh". I noticed, however, that the facsimile of the title page revealed that the book was published by the Nottingham Journal Offices in Nottingham. I made some research into the life of the author, and I quickly learned that he served on the Honorary Staff of the General Hospital, Nottingham, my own hospital, and I was able to establish that in every sense he was a citizen of Nottingham, and certainly not "a man of Edinburgh".

SOME BIOGRAPHICAL DETAILS

Dr. John Calthrop Williams was the son of a doctor, Dr. William Williams.

There is in the possession of the Nottingham Public Library a copy of "A Compendious Chyrurgie" by the famous mediæval surgeon John Banester, himself a man with Nottingham associations. It bears the date, 1585; in the blank pages and in the margins are many notes written in quaint English handwriting. One wonders if the name on the fly-leaf, William Williams, is that of the father of John Calthrop.

After receiving his education at Repton under the Reverend W. Boulthee Sleath the future Dr. John Williams returned to Nottingham and began his medical training as a pupil of Dr. Marsden at the General Hospital, before proceeding to Edinburgh where he graduated in August 1824. He first practised in Sheffield at No. 1 Norfolk Row, and it is recorded in a diary of Thomas Asline Ward of Sheffield that " Dr. Williams, lately come to Sheffield, was admitted a member of the Book Society". In 1825, as a result of the death of Dr. Pennington, he returned to Nottingham where he lived until his death.

In 1827 he published a pamphlet, an original copy of which is still available in the Public Library, entitled, "A letter to the Governors of the Hospital, being a brief collection of medical evidence, proving the safety and propriety of establishing fever wards in connexion with general infirmaries". The pamphlet was printed by H. Burnett of High Street, Nottingham. For a doctor of only three years' standing it is a remarkable little pamphlet. He showed a wisdom and maturity that one would expect only from a more experienced man, especially in the way he obtained and collected together the written opinion on the advisability of setting up of fever wards, from the best-known medical men of London and all over the country. He must already have made some little name for himself, as on the cover he is described as, "Extraordinary Member of the Royal Medical Society, Edinburgh".

In the Parish Church of Wollaton, in the marriage register, we read that John Calthrop Williams, M.D., of the Parish of Saint Peter in the Town of Nottingham, bachelor, and Anne Sanders of that Parish, spinster, were married there by licence on the first day of October 1829 by John Wolley, Vicar of Beeston. Six members of the family signed the marriage entry. In the baptismal register of this church are entered the names of two little girls of theirs, Mary, born February 14, 1834, and Adelaide Elizabeth, born March 7, 1836. Both of them died in infancy. In the Baptismal Register for St. Peter's Church, Nottingham, is recorded the baptism of five more children. William Rhys on August 23, 1837, George Sanders on March 22, 1839, Anne on December 8, 1841, Charles John on April 8, 1844, and John Herbert on April 13, 1845. His address from 1837–1839 is given as Rose Place and in '41 and '45, Low Pavement.

About 1833–1835 a Medical School was established in Nottingham with premises in St. James' Street, and in his book on Palpitation of the Heart, Williams states that the material in the book was originally a course of lectures he gave there. He describes himself as "Lecturer on the principles and practice of Physic". Despite such a distinguished patron as the Duke of Newcastle, the idea of a Nottingham Medical School soon fell through and by 1836 Williams speaks of it in the past tense.

From the directories of Nottingham of 1844 it is learnt that Dr. Williams, magistrate, owned his

house in Low Pavement, freehold. It is also stated that he was President of the Literary Society which met in the Assembly Rooms, Low Pavement.

In 1851 Williams was involved in High Court litigation, Williams and Chouler v. Cursham. There is a copy of the Judge's summary and verdict in the British Museum: it makes most interesting reading. Judgment was delivered for Dr. Williams and Mr. Chouler. They had been appointed trustees and executors, and with certain charities, residuary legatees. Cursham opposed probate on the grounds that the testatrix, a Miss Boote of Nottingham, had been unduly influenced to change her will. An earlier will had been in favour of her niece, a Miss Jane Frances Grey, afterwards Mrs. Cursham. Dr. Williams received about £12,000.

Between 1850 and 1853 Dr. Williams moved to Wheeler Gate where he lived until his death. Some fifteen years previously, the first Municipal elections were held and in 1835 Dr. Williams was returned as Conservative for the Exchange Ward: he sat on the Council for two years.

Dr. Williams was elected to the Provincial Medical and Surgical Association in 1841 and was a Member of Council 1842–1853. Presumably he played some part in the negotiations for merging the Provincial Medical and Surgical Association and the British Medical Association, but no definite evidence of this has so far been traced.

Dr. Williams suffered from chronic asthma during the later years of his life and, as a result, his practice had to be much contracted. His death was tragic. As a busy townsman he came into contact and made friends with both the humble and exalted of this world. One of his friends was Lord Middleton of Wollaton Hall. On a Sunday evening in July 1856 he left his own home in Wheeler Gate and drove to dine with Lord Middleton. Dr. Williams left the Hall later, his carriage being driven by his groom. Going up the steep hill from Lenton, after a touch of the whip the horse began to plunge and kick and then got one leg over the shaft. After a few yards the driver again had the horse under control but then to his horror found Dr. Williams was not in the carriage, he was lying some distance away in the roadway. He had sustained a compound fracture of the skull and was attended by Dr. Henry Taylor, by Mr. J. L. Thompson, the Surgeon, and Dr. R. S. Hutchinson. These three men sat with him all night and were with him until he died the following morning.

The England of His Day

The war with France, begun in 1778, had run a protracted and ruinous course. The Napoleonic decrees had curtailed British manufactures, the price of food had gone beyond the reach of many, and there was great unemployment. There were repeated riots on account of poverty, and there were both individual and civic efforts to relieve the appalling distress. Life was held cheaply and justice was brutal and stern. Public hanging was the rule and the place of execution in Nottingham was either Gallows Hill, a place some half a mile on the main road going north out of the town, or the road immediately in front of the Assize Court. Commonly the body was later removed to the mortuary of the General Hospital for dissection and public exposure.

In 1811 there began those outbursts of Luddite violence which persisted for several years in Nottingham and the surrounding districts. Towards the year 1795 thousands of men and women weaving goods on looms in their own homes were rendered unemployed by the coming into existence of huge buildings, which we now call factories or mills, where machine-operated looms did the work of these people in a fraction of the time. Consequently there arose for many of them unemployment, and reduction in wages of stockingers. After a warning notice signed by "Ned Lud", a raid was undertaken to smash the frames of the master hosiers. This raid was conducted with almost military precision under their leader, and relatively few Luddites were caught. Laws were passed in Parliament against the framebreakers, making their crime punishable by death instead of by transportation. Lord Byron, with his Nottingham association, violently opposed these measures in the House of Lords, ascribing the outbreak to unparalleled distress. The Mayor and Corporation, however, appointed a secret committee which was empowered to pay large sums of money to anyone who would lodge information about the activities of the dreaded Luddites. About £2,000 was granted for this purpose.

1819 was a year of most terrifying hardship. A procession of 5,057 men on one occasion marched through the streets of Nottingham carrying banners bearing the words, "We ask for bread", and "Pity our distress". A petition was addressed to the Lord Lieutenant of Nottingham by the organisers stating that, after working from sixteen to eighteen hours a day a skilled worker could not earn more than from four shillings to seven shillings a week. The Vagrants' Office, instituted by a number of benevolent gentlemen, was opened and in its eighteen years of life some 25,000 persons were given some measure of relief and lodging.

In 1831 there was a great uprising and Nottingham Castle was fired by the mob. At this time the Reform Bill was greatly agitating the public mind. A report reached the town that the Lords had rejected the Bill, and immediately a wave of resentment and excitement swept through the town. While disturbances at Derby some sixteen miles away had drawn off the military, the mob collected and looted first Colwick Hall, and then flushed with success returned to the town, and failing to break into the House of Correction and release the prisoners, stormed its way into the heart of the city itself, invaded the Castle, then the home of the Duke of Newcastle, and set it on fire. The castle is

perched on the summit of Castle Rock and the flames could therefore be seen for miles around, and patients and doctors in the General Hospital, actually adjacent, could have watched each stage of the attack.

The Chartist Riots, beginning in 1839, broke out again and again for three years. Once Dr. Williams and four other men bravely went out to meet the mob, reasoned with them and told them that they must at once disperse or prepare for the consequences. Although the men received the news with groans, on that occasion the eloquence of Dr. Williams made the crowd disperse.

In his boyhood there was a plague of smallpox, the centre of the town being worst affected, and the mortality was as high as one in three. In later years there was an outbreak of Asiatic cholera; 900 persons were affected and 300 died.

During his lifetime Dr. Williams saw two revolutions of another kind in the life of the town; these were the installation of gas as a form of street lighting, and the opening of railways from Nottingham to Lincoln, to Derby, and to London. He witnessed the festivities in the town in 1820, celebrating the withdrawal of the Bill of Pains and Penalties against the Queen. He witnessed the great rejoicings of the triumph in the fight for human freedom—the emancipation of the negro slave. And yet strange as it may seem, in the market place in 1808 a man was put in the pillory—the last time albeit that this punishment was carried out. Furthermore in the market place of the city in the year 1852 and again in 1853 there was committed the monstrous and unpunished crime of a man selling his wife—the price being not even thirty pieces of silver but just one.

Life in the Hospitals in the First Half of the Nineteenth Century

Dr. Williams served on the Staff of three Nottingham hospitals, the General Hospital, the Dispensary and the General Lunatic Asylum.

The General Hospital, Nottingham (Fig. 1). The Minutes of the weekly meeting of the House Committee written in careful copper-plate hand, describe a picture of hospital life, incredibly different from that of the present time. The hospital was lit by candlelight, the bills for which were examined weekly at the Hospital Committee. Patients lay at night in wards lit only by rush light, and nurses went their rounds holding a lighted candle in their hands as they leaned over the patients' beds.

Fig. 1.—The General Hospital, Nottingham (about 1800).

In 1835, it is recorded that a patient had his name placed in the Black Book. This offence meant that he could never be readmitted because he was caught lying in bed reading by candlelight.

By 1839, gas had been installed in some wards, but it was several years before the whole hospital could benefit by this startling innovation.

As a commentary on the standard of hygiene and sanitation of the time an entry in the Minute Book for 1843 is interesting. An order was given for a wall in the ophthalmic ward to be broken down and a window in another wall to be built up because of the stench of the pigsties outside that window. The state of the mortuary can be faintly imagined from the fact that at the Nottingham Assizes of 1844, the judge commented in Court on its dreadful stench, and the Hospital Committee thereupon authorized the erection of a new "Dead House".

Nurses had not reached professional status. They received wages not a salary; we know, for instance, that the wages paid to the nurses was four shillings and sevenpence a week for a woman and five shillings and ninepence for a man. The Matron's salary was raised in 1840 from £40 to £50 a year.

Dr. Williams was appointed Physician to the General Hospital in 1839 and held that post until 1851. There was a practice of accepting pupils at the hospital from time to time, and the fees varied between £250 to £300. Dr. Williams had four pupils under his care and guidance. The bare records of his attendances as Physician for the week give but little indication of all the work he must have done at the hospital. It is only when one reads his name among the list of those on special committees called to deal with cholera cases, or difficulties of staffing, &c., that one appreciates the position of trust he held.

The Nottingham Dispensary was the second institution in which Dr. Williams served and indeed it was founded with his active help.

On December 16, 1830, a petition signed by 80 inhabitants appeared in the local press. This asked the Mayor to call a public meeting to consider the advisability of establishing a Dispensary. The Mayor promptly responded by summoning the citizens of Nottingham to a public meeting to be held at the Exchange. The meeting was well attended and several resolutions were passed. One was "that a Dispensary should be opened for the daily admission of Out-Patients"; another, "that arrangements should be made for visiting patients under particular circumstances, in their own houses", and a third, "that a building be secured in the central part of the Town".

The response was almost immediate and most generous for, in the following month, January 1831, the first list of donations and subscriptions appeared in the papers; but very quickly the Committee became alive to the fact that there appeared to be trouble and dissatisfaction in the ranks of the medical profession about the organising of the work of this newly planned Dispensary. An emergency committee meeting was held at the Exchange on January 12 to voice this dissatisfaction, and it was unanimously resolved "that the impression said to prevail in the town that members of the medical profession have been excluded by the Dispensary Committee is incorrect, no such resolution having been passed, and the Committee considering that the view of the public meeting in abstaining from appointing in the first instance any medical gentlemen as members of the Committee, was solely to prevent any apprehension of undue preference being shown, and not from any wish to exclude the members of that profession; and finding that the view has been misunderstood do now appoint the three Senior Physicians and the three Senior Surgeons resident in Nottingham together with Dr. I. M. Davidson and Dr. J. C. Williams as members of the Committee".

The Committee now decided to have a Ball to raise money, but the result was not a financial success. As a note in the Press diplomatically states: "The Ball was not numerically attended, but the Company was select and fashionable". The subscription list slowly mounted. Honorary physicians and honorary surgeons were elected, among them Dr. Williams. In May 1831 the Dispensary was opened at a house in Hockley.

For some years Dr. Williams remained zealous and keen on the dispensary work. Under his direction a new building was being planned, and special funds were being raised for surgical aid, and for the caring of people at home. He aimed to have a building near the Dispensary where people could have after-care treatment, and where there would be a lying-in ward, with resident nurses. Unfortunately his idea was not welcomed by the Committee. He resigned fairly soon afterwards. We conclude, therefore, that the Governors were neither as far-seeing nor as enlightened as Dr. Williams.

The General Lunatic Asylum, Nottingham, was the third institution in which Dr. Williams served. Interest in lunacy seems to have been a family affair, as his own father worked there for twenty-three years, and Dr. J. C. Williams' son became one of the first of the Lunacy Commissioners for England.

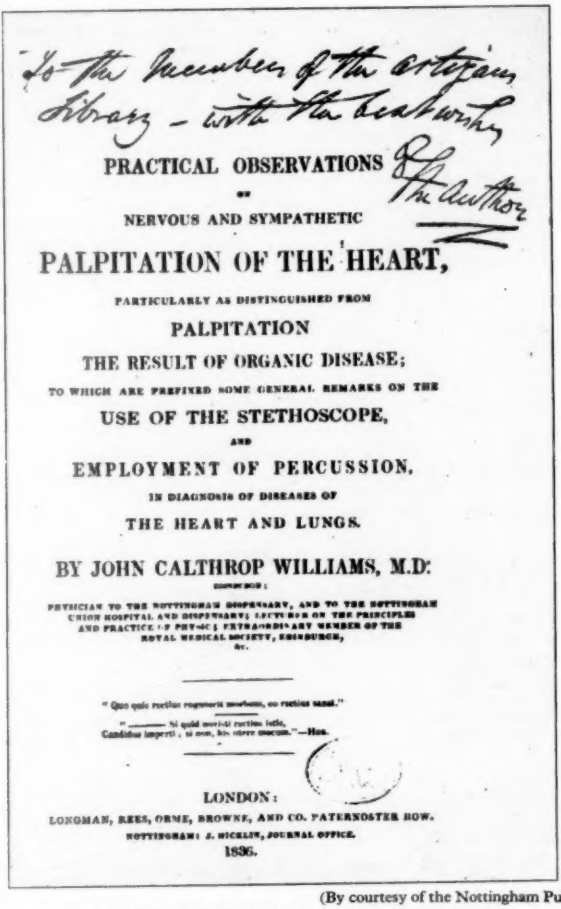
Our Dr. J. C. Williams served the Asylum for some twenty years, and the treatment of patients there must have been good. In the Asylum there was no case of the Asiatic cholera which was raging in England in 1849. The Lunacy Commissioners paid their first visit during Dr. Williams' office, and recorded their satisfaction with the work done.

Dr. Williams' duties appeared to require his attendance there the forenoon of every Wednesday, and at other times as required. For this he received a fee of one guinea every half-year for each patient admitted.

His Important Book

Dr. Williams' chief title to fame is his book of which two editions were published, one in 1836 (Fig. 2), and the second in 1852. Early in the nineteenth century, Corvisart, Napoleon's Physician,

declared that heart disease was, with the single exception of pulmonary tuberculosis, one hundred times the most common of all organic diseases diagnosed by doctors in public and private practice in France. It was against the background of this orthodox opinion that Williams wrote this book, with the purpose of demonstrating quite briefly the fact that the symptom of palpitation is not



To the Members of the Artizans Library - with the best wishes of the Author

PRACTICAL OBSERVATIONS

ON

NERVOUS AND SYMPATHETIC

PALPITATION OF THE HEART,

PARTICULARLY AS DISTINGUISHED FROM

PALPITATION

THE RESULT OF ORGANIC DISEASE;

TO WHICH ARE PREFIXED SOME GENERAL REMARKS ON THE

USE OF THE STETHOSCOPE,

AND

EMPLOYMENT OF PERCUSSION,

IN DIAGNOSIS OF DISEASES OF

THE HEART AND LUNGS.

BY JOHN CALTHROP WILLIAMS, M.D.

CONSULTING

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"Quo quis rectius cognoverit morbum, eo rectius sanat."

"——— Si quid novisti rectius istis,
Candidus imperti; si non, his utere mecum."—Hor.

LONDON:

LONGMAN, REES, ORME, BROWNE, AND CO. PATERNOSTER ROW.

NOTTINGHAM: J. SICKLIN, JOURNAL OFFICE.

1836.

(By courtesy of the Nottingham Public Library)

FIG. 2.—The title page of Dr. J. C. Williams' book.

important. The book is entitled "Practical Observations on Nervous and Sympathetic Palpitation of the Heart". Williams gives an early chapter to "Sympathy". "To speak accurately", he says, "the word sympathy means fellow-feeling or fellow-suffering". The principal organs of the body are highly complicated affairs. The functions performed by one organ are not of a simple kind. Parts at a distance with no seeming connexion, either at all times, or on extraordinary occasions, contribute to the integrity of the body. This relation he calls "natural sympathy". An impression on one organ gives rise to an effect on another, without physical influence, or any effect on intermediate parts.

Some sympathetic acts are instinctive efforts of nature to remove a noxious agent, for example, the cough in bronchitis to remove the phlegm; the sighing in sorrow to relieve the congested state of the heart produced by profound grief. In addition to "natural sympathy" there is a "morbid sympathy" which is produced by injury or disease; thus a blow on the head causes vomiting. Then there are other sympathies—involuntary ones, those arising from emotion, instinctive ones, and those that act on the organs of secretion. He says "it were a mere waste of time to enter into any dissertation on the intimate nature of sympathy: we cannot understand the how, but we can understand the why". Coming to the heart, he regards that as acting as a reservoir of blood as well as a propelling mechanism,

hence any alteration in the fluid held by the heart will derange the heart, and a striking example of this is anæmic palpitation. Mental emotions are a frequent cause of sympathetic disturbance, of which joy and anger are frequent examples. These emotions cause palpitation. The heart is more intimately connected with the lungs than any other organ, hence one would expect the sympathy between them to be strong. The sympathetic influence between the stomach and the heart is also great. Hence, palpitation is a common concomitant of derangement of the stomach and intestinal canal, and it is thus easy to understand why flatulence and intestinal worms are common causes of palpitation.

Palpitation he defines as an awareness of a temporary augmentation of the speed of the heart and he gives the condition a double ætiology. First, primary palpitation, which he describes as arising from the heart itself, and which may be found in individuals who, accustomed to sedentary occupation, have indulged in vigorous exercise. And, secondly, sympathetic palpitation, which is found in persons of nervous temperament, and such persons he says often produce symptoms which baffle all attempts at explanation. How true is that remark! Palpitation, he points out, can be produced also by fevers, by anæmia, and by an irritability of the nervous system. In these conditions there is often found associated, in the female, hysteria or anæmia, in males, hypochondriasis or a melancholic tendency. "No persons", says Williams, "are liable to this affection more than those who have dabbled in physic. If such persons have their thought directed to the state of the heart, they are sure to become victims of nervous palpitation."

There is a long chapter devoted to treatment, and his advice is exemplary in his insistence on seeking and removing the primary cause. Blood-letting, and the use of purgatives and emetics are described as having a value in the chosen case. The drugs he advocates may still be used to-day. His advice on exercise was probably surprising to his contemporaries, but to our ears it is the wording of his advice which seems quaint: "it is imperative to enforce a steady plan of exercise, on foot, on horseback, or in a carriage according to the patient's habits of life."

My researches into the life and background of this physician have proved of deepening interest. There has gradually been built up for me the picture of a wise doctor whose counsel was sought by many, and of a man of great courage who did not yield to opposition from his fellow doctors when he was sure his opinions were right. Above all I have found and saluted an original thinker who has given to the world new light on the diagnosis of disorders of the heart.

I am happy to acknowledge the very great help of my sister, Mrs. R. Hayes, M.A., in the preparation of this paper.

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[*April* 7, 1954]

Sir John Burdon Sanderson

By Sir ARTHUR S. MACNALTY, K.C.B., M.A., D.M., F.R.C.P., F.R.C.S.

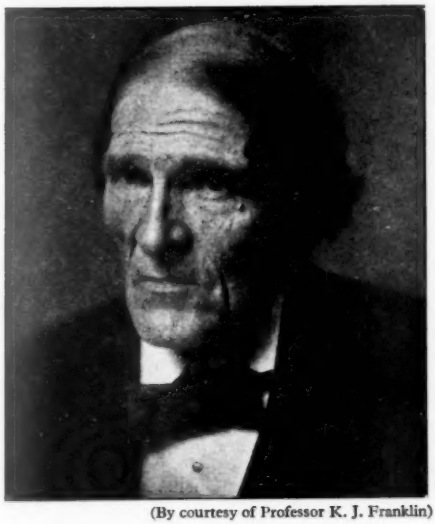
SOME men bear the imprint of their intellect in their features and by the very force of their personality stand out from their fellows. Of such was John Burdon Sanderson. I remember in my first term as an undergraduate at Oxford meeting him as he came out of the Museum. Although I did not then know him, the tall thin figure in cap and gown, the clear-cut features, the piercing eyes, made an unforgettable picture on my visual memory. "That is one of the great men of the University", I said to myself and later realized that I had seen "the Burder", as the Regius Professor of Medicine was affectionately called.

BIRTH AND MEDICAL EDUCATION

The Burdons were an old Northumbrian family. They were county squires with some interest in commerce. Richard Burdon went to Oriel College, Oxford, gained the Newdigate prize in 1811 for a poem on the Parthenon, took a first class in *Literæ Humaniores* in 1812 and was Fellow of his College. In 1815 he married Elizabeth Skinner Sanderson, the only child of Sir James Sanderson, Bt., banker and hop-merchant, Sheriff and twice Lord Mayor of London, in accordance with whose will he took the name of Sanderson. Of their five children John Scott Burdon Sanderson was the second son and fourth child. He was born at Jesmond, near Newcastle-on-Tyne, on Decemb-

21, 1829, his father having abandoned a promising legal career to live in Northumberland on his property. John's sister, Mrs. Haldane, described him as "a beautiful child, very fair with bright auburn hair and large deep blue eyes". As a boy he was a keen naturalist, quick at his books, a lover of music and singing and played the violin. He was taught partly by his father and partly by tutors and early made his choice to study medicine.

In 1847 he matriculated at Edinburgh University. His chief teachers were Balfour for botany, Goodsir for anatomy and Hughes Bennett for medicine. Throughout his life Burdon Sanderson was an ardent botanist. His first scientific paper read before the Edinburgh Medical Society in 1848 treated of the irritability or excitability of plants, a subject which he carefully investigated in later life. As a student he is described as tall, erect and dignified with an intellectual countenance, "habitually grave, as if his thoughts were always fixed on his studies, but readily relaxing into a pleasant smile when he entered into conversation". In 1851 he received the degree of M.D., his thesis, entitled "On the metamorphosis of the coloured blood corpuscles", being awarded a gold medal.



(By courtesy of Professor K. J. Franklin)

FIG. 1.—Sir John Burdon Sanderson.

Paris was then the chief centre for postgraduate studies and thither Burdon Sanderson went in the autumn of 1851. He studied organic chemistry with Gerhardt and Wurtz, embryology with Coste and physiology under Claude Bernard, and attended the Paris hospitals. He was greatly influenced by Bernard's teaching. In 1852 he settled in London and on August 9, 1853, he married Miss Herschell. Shortly afterwards, he was appointed Medical Registrar to St. Mary's Hospital and in 1854 Lecturer on botany, a post which he exchanged in 1855 for the lectureship on medical jurisprudence. This appointment he held until 1862 and the Registrarship until 1858. In 1855 he took the M.R.C.P., becoming F.R.C.P. in 1871. In 1878 he was Harveian Orator. In 1860 he became assistant physician to the Brompton Hospital for Consumption and Diseases of the Chest, later becoming full physician. He was assistant physician to the Middlesex Hospital from 1860 to 1870 and lecturer on pathology there.

WORK IN PUBLIC HEALTH

Burdon Sanderson became interested in the new field of organized public health, and in February 1856 was appointed Medical Officer of Health for Paddington, under the Act of 1855 requiring that Medical Officers of Health should be created for all districts of the metropolis. The salary was £300 per annum, but Burdon Sanderson gave the Paddington Vestry much more than part-time service. His diaries are full of entries relating to inspections of dwellings where "nuisances" of various kinds existed and of visits to slaughterhouses, cowhouses and bakehouses. He presented fortnightly reports and quarterly summaries of his work to the Sanitary Committee of the Vestry in addition to printed annual reports. He struggled to improve the unhealthy condition of the Regent's Canal Basin and that of the wharves on its banks. The Canal Basin was drained on two occasions, and in 1865 it

was noted that the health of the inhabitants had improved. But there was no means by which the Canal Company could be compelled to keep the water pure! In cleansing the Serpentine from sewage contamination Burdon Sanderson was more successful. He advocated public slaughterhouses, a reform which has only been effected on a large scale in recent years. He looked after the bread and milk supplies of the district and served on a Whitehall Commission on adulteration. By his tact and courtesy he often got insanitary housing conditions remedied without recourse to legal action. On two occasions he had to deal with outbreaks of cholera. He also made numerous experiments on ventilation and improved the ventilation of the wards of St. Mary's Hospital. At the same time he was engaged in consulting practice and hospital work and was a member of several medical societies. Any interval of leisure was given to scientific investigations. In 1867 he ceased to be Medical Officer of Health, as other duties claimed the whole of his time and attention.

Investigations for the Privy Council

Sir John Simon frequently utilized Burdon Sanderson's services in investigations for the Medical Department of the Privy Council. With Dr. Greenhow from 1857 to 1860 he investigated diphtheria, then a rare disease, at seventy centres in England where it had appeared. He referred to this early work in his Croonian Lectures to the Royal College of Physicians in 1891. From 1860 to 1865 Burdon Sanderson was a medical inspector under the Privy Council. He inspected vaccinations and investigated outbreaks of smallpox and cholera. In 1865 his report on cerebrospinal meningitis in North-east Germany gave a very full account of the history, epidemiology and symptomatology of the disease. It was the first report on the epidemiology of this condition. In 1867 he was elected F.R.S. He gave the Croonian Lectures on the influence of respiratory movements on the circulation based on experimental studies.

Researches for the Privy Council

Burdon Sanderson took an important part in research work for the Privy Council. In 1865, in his work for the Experimental Committee of the Royal Commission on Cattle Plague, he made his first personal contribution towards the elucidation of the infective processes. He showed that in artificially inoculated animals, whenever the earliest manifestations of disease were present, the blood was already infective for other animals. Koch in 1896 wrote to Burdon Sanderson that this work was long known to him as the best ætiological and pathological study of cattle plague that had been made. Burdon Sanderson noted that the infective agent did not diffuse through parchment paper; this led him to entertain the possibility of some infective agents being not only particulate bodies but also ultra-microscopic.

In 1867 and 1868 he confirmed Villemin's work as to the inoculability and transmission of tuberculosis in experimental animals; although expressing no views as to the nature of the infective agent, he did not exclude a specific contagium of tuberculosis. His careful microscopic study of the lesions experimentally produced were in great part confirmed by modern investigations with improved microscopic methods.

Burdon Sanderson's further work during 1869 to 1872 dealt with the consideration of contagion, wound infection and the pathology of blood poisoning. He showed that acute septicæmia and chronic pyæmic conditions in which abscess formation predominated were both manifestations of blood poisoning, and rightly identified bacteria, especially round forms (pyogenic cocci) as the causal agents.

In the later 'seventies, while head of the Brown Institution, he studied pleuropneumonia and anthrax, in both researches suggesting the possibility of protective vaccination. If he had pursued these researches, he might have advanced immunology by a number of years. Even to-day his papers on infectivity, the febrile process and tuberculosis are deserving of careful study, both as masterly grouping of the then known facts and for the original work they contain.

Autopsy on the Emperor Napoleon III

After the death of the Emperor Napoleon III at Chislehurst in 1873, Sir Henry Thompson, as Sir Zachary Cope tells us in his biography of Thompson, in consultation with Sir William Gull and the French doctors, proposed that an autopsy should be made by some distinguished professor of pathological anatomy, and it was unanimously agreed that none at that time had so high a reputation as Professor John S. Burdon Sanderson. He performed the autopsy on January 10 and his full and careful report showed that the Emperor had extensive disease of both kidneys and that some calculi were still present in the bladder after Thompson's operation. The doctors expressed the opinion that the disease of the kidneys was of such a nature and so advanced that it would in any case have shortly determined a fatal result.

The Physiologist

As we have seen, Burdon Sanderson had an intense interest in pathology, and he did more than anyone else to establish a living school of pathology in this country. But now physiology began to occupy more and more of his time, and in 1870 he was appointed Professor of Practical Physiology and Histology at University College, London, in succession to Michael Foster. In April 1874, on

Professor Sharpey's retirement, he became Professor of Physiology, the two chairs being merged into one. He had as his assistant Professor Schäfer. From 1871 to 1878 he was also professor-superintendent of the Brown Institution, University of London.

Burdon Sanderson's *Handbook for the Physiological Laboratory*, a work in two volumes, consisting of four sections written respectively by Klein, Burdon Sanderson, Foster and Lauder Brunton did a great deal to develop the study of physiology in this country. Burdon Sanderson's own section was concerned with blood, circulation, respiration and animal heat.

At University College he worked indefatigably, as usual, removing from 49, Queen Anne Street to 26, Gordon Square, in order that he might be near his work. "The day's work began long before breakfast time, and it was continued till the evening." Amongst those who carried out researches under his direction were Sydney Ringer, G. J. Romanes, Victor Horsley, F. W. Mott, Patrick Geddes, Francis Gotch, J. Rose Bradford, W. M. Bayliss, A. D. Waller, William Osler, F. A. Dixey, Newell Martin, F. J. M. Page, and Edward Schäfer, a truly illustrious company. Burdon Sanderson was always a source of inspiration to his students.

University College was one of the first schools of medicine to bring laboratory work into the teaching of science in an organized and developed form; and, after Sharpey, Burdon Sanderson had a leading part in carrying these new conceptions of medical education into effect. The Physiological Society was founded in 1876 with the active support of Burdon Sanderson, Foster and the younger men who came under their influence.

It was at University College that Burdon Sanderson began in 1875 his researches on the mechanical effects and the electrical disturbance consequent on excitation of the leaf of *Dionæa muscipula* which formed the subject of his Croonian Lecture in 1877. Five years later in 1882 he published a more extended and detailed account of the phenomena in the *Philosophical Transactions*, entitled "The Electromotive properties of the Leaf of *Dionæa* in the Excited and Unexcited States." A third paper on the same subject appeared in the *Philosophical Transactions* of 1888. He pursued the same method of inquiry in the cardiac muscular tissue of the frog (*J. Physiol.*, 1880, **2**, 384). These researches have been taken as a model for subsequent electrophysiological investigations on different tissues.

The Oxford Professor

In 1879 and 1880 Burdon Sanderson was an examiner in the Honour School of Natural Science at Oxford. This brought him into close touch with Sir Henry Acland, Regius Professor of Medicine, who was reviving medical studies there. In 1882 Burdon Sanderson was persuaded by Acland to carry the torch of physiology from University College to Oxford, as Foster had done when he went to Cambridge, and as Schäfer was to do at Edinburgh. Accordingly, he became Waynflete Professor of Physiology and a Fellow of Magdalen College. A few months later he settled in a house in Banbury Road, Oxford.

On his arrival he was plunged into a storm of controversy which was repugnant to his retiring disposition, but in which he bore himself with dignity and courage. In founding the chair of physiology no provision had been made for the necessary laboratories and equipment. In February 1883, Convocation voted him without question £1,500 for instruments and apparatus, and three months later notice was given of the intention to ask Convocation to vote £10,000 for the erection of a physiological laboratory at the Museum. This raised a storm of opposition, partly from the economists, who objected to such great expenditure on buildings for science, but especially from the anti-vivisectionists, headed by Professor Freeman, who opposed the establishment in Oxford of a "Chamber of Horrors". As for vivisection experiments, they were unnecessary for scientific teaching: the historian might equally claim to illustrate the siege of Jerusalem by reproducing its massacres or the Elizabethan festivities of Kenilworth by a bull-baiting. After a strenuous debate in which Acland and Burdon Sanderson took part, the decree was carried by a majority of three. The struggle for physiology at Oxford was prolonged; and Sir William Church wrote that he would never forget Burdon Sanderson's striking face and figure as he stood quietly leaning against the wall of the Sheldonian Theatre during the momentous debate on February 5, 1884.

Having weathered this tempest, the Oxford ship of physiology sailed into calm waters. Here, as in London, Burdon Sanderson's fame brought him assistants and friends in his work. Francis Gotch (who afterwards succeeded him as Professor of Physiology) and F. A. Dixey (who became tutor and Fellow of Wadham College) accompanied him from University College, London. In 1887 Burdon Sanderson's nephew, John Scott Haldane, came and began to teach chemical physiology. Other famous pupil physiologists were G. A. Buckmaster, Stanley Kent, M. S. Pembrey and Leonard Hill. In private research work Burdon Sanderson was assisted by G. J. Burch, Florence Buchanan (daughter of his old friend, Sir George Buchanan the elder) and for the last three years of his life by H. S. Souttar (now Sir Henry Souttar), eminent in physics as afterwards in surgery, who helped with a photographic recording apparatus for the capillary electrometer. Besides these, many Oxford pupils or friends from elsewhere made researches in the Department of Physiology which soon made the Oxford medical school famous.

Researches into muscle and nerve absorbed the Waynflete Professor and entered largely into physiological teaching during his and Gotch's tenure of the professorship. Burdon Sanderson's

lectures were frequently above the heads of his most advanced students. His intellectual powers were so great that he often assumed a perception in his audience that was lacking, and his exposition was frequently obscure for this very reason. We students in the Honour School of Physiology sometimes thought that the kymograph, electromotive force and stimulation of nerves and muscle fibres bulked too largely in our curriculum, but I understand from my friend, Sir Charles Lovatt Evans, that much of Burdon Sanderson's work is now being revived and forms the basis of some modern physiological research.

Although Burdon Sanderson devoted what time he could to teaching and research work, there were many calls upon him. He had to participate in University business, and was frequently summoned to London to serve on committees and Commissions. Thus he served on the Commission on Hydrophobia in 1886–7, of which Victor Horsley was the energetic Secretary; this confirmed the results of Pasteur's experiments. He also served on the Royal Commission on the University of London, 1892–4, and on the Royal Commission to inquire into the effect of food derived from tuberculous animals, 1890–5. He took an active part in the founding of the Lister Institute and served on an inquiry made by the Board of Agriculture into the landing in Great Britain from Canada of cattle affected with pleuropneumonia. In 1893 he was President of the British Association which met at Nottingham. The subject of his Presidential Address was "The Origin and Meaning of the term 'Biology'," and Dr. Haldane said it was so stored with intellectual knowledge that many biologists found it beyond their grasp.

The Regius Professor

On the resignation of Sir Henry Acland in 1895, Burdon Sanderson became Regius Professor of Medicine and was elected an Honorary Fellow of Magdalen College. The post brought with it new responsibilities. One of his chief aims was to develop the teaching of pathology in the University. In 1895 he had arranged for a complete course of instruction in pathology and bacteriology extending over the three terms of the academic year and himself delivered twelve lectures in the course. He was continually pressing for the provision of a Department of Pathology at the Museum. In 1897 he secured the help of Dr. James Ritchie, who was first Lecturer, then Reader and finally the first Oxford Professor of Pathology, the desired Department being built at a cost of £10,000. Dr. Ewan Frazer, one of the early students, contributed half this sum and the University the other half. Burdon Sanderson also participated in the management and work of the Radcliffe Infirmary, and in many ways laid the foundations of the present-day flourishing medical school. His great services to medical science were recognized by the bestowal of a baronetcy in 1900, and he received many honours from British universities and scientific and medical societies.

In 1904 failing health compelled him to resign the Regius Professorship. In doing so, he made a great gift to Oxford, for it was at his request and to his gratification that William Osler, his old pupil, succeeded him.

After several months of increasing physical weakness, Sir John died at Oxford on November 23, 1905, and was buried in Wolvercote cemetery. Lady Burdon Sanderson survived him until July 5, 1909. They had no children and the baronetcy became extinct at his death.

Conclusion

In his industrious and useful life, Burdon Sanderson was a great benefactor to medical science and to mankind. His profound knowledge at times made him over-cautious; and in his work on tuberculosis and on the intimate pathology of contagion (Appendix to Sir John Simon's Report to the Privy Council, 1869) he halted on the threshold of great discoveries in bacteriology and immunology. Nevertheless, in this last-mentioned report he gave prophetic intimation of the causal relationship of specific organisms to disease.

In his later years he devoted himself to physiology and pathology. As Professor F. Gotch observed: "In physiology he was an acknowledged master in his own somewhat recondite branch of physiological research; he founded an English school of exact experimental work and initiated new methods of teaching. . . . In pathology he powerfully enforced the truth that experimental investigations are essential for the elucidation of pathological problems, and that sound pathology must rest on an accurate physiological basis." These truths were first given to the world by William Harvey, but it needed a man like John Burdon Sanderson to apply them to medicine in the nineteenth century.

I am indebted to Sir Humphrey Milford and the Clarendon Press, Oxford, for kind permission to make use of material from the Memoir of Sir John Burdon Sanderson published by them.

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Infectious Mononucleosis

A Review of the Condition as Seen in the Royal Navy

By Surgeon Commander M. A. RUGG-GUNN, R.N., M.A., M.D., M.R.C.P.

GLANDULAR fever appears to have been first mentioned in the Royal Navy in 1931 when one case was recorded in the Home Fleet. No further cases are mentioned until 1934 when a case, also at home, was diagnosed. In 1935 there were 2 cases, one in the home station and one in China, in 1936, 5 cases (4 at home and 1 in China), and in 1937, 4 cases (3 at home and 1 in the Mediterranean). After this the condition became progressively more frequently diagnosed, though exact figures for the war years, when, of course, the population at risk was greatly increased, are not available. This increase has in the main continued, until at present it has come to rank second only to rubella amongst the zymotic infections if we exclude the common cold and influenza groups, as Table I shows.

Even allowing for better facilities in diagnosis and a greater awareness of the disease this increase is truly remarkable, and the purpose of this paper is to review glandular fever, as seen in the Royal Navy at home during the years 1948 to 1953 inclusive, considering all aspects of a disease which already ranks as a major factor in the wastage of man-hours. The condition appears to be much more prevalent at home than abroad, and ashore than afloat; this last fact may be due to the younger and more susceptible age-groups being employed ashore for training.

ÆTIOLOGY

Age.—Originally glandular fever was considered a disease of childhood, but there seems during the past few decades to have been an increased tendency for adults to be affected. In the isolated community of the Falkland Islands, Moir (1930) found that 10% were aged between 45 and 65. The youngest recorded appears to be 7 months (Davis, 1929).

In the present series the age incidence is as follows:

Age	Number of cases	Age	Number of cases	Age	Number of cases	Age	Number of cases
15 ..	10	22 ..	30	29 ..	3	36 ..	1
16 ..	9	23 ..	26	30 ..	4	37 ..	1
17 ..	12	24 ..	17	31 ..	1	38 ..	0
18 ..	45	25 ..	10	32 ..	3	39 ..	1
19 ..	84	26 ..	4	33 ..	0	40 ..	1
20 ..	72	27 ..	5	34 ..	1	41 ..	1
21 ..	64	28 ..	6	35 ..	1		

This series represents a selected age group in that children under 15 are excluded and adults over the age of 45 only represent a small proportion of the armed forces; allowing for this over 80% fell within the 18 to 25 age group.

Season incidence.—The monthly intake of cases was as follows:

January .. 27	April 29	July 42	October .. 37
February .. 41	May 42	August .. 29	November .. 22
March .. 36	June 48	September .. 36	December .. 23

The figures for July, August and September are lower than would be the case if the Naval population was quite constant, as many ships are away from port on cruises and exercises, and the summer leave is given during this period. The sea-going ships represent a variable but small proportion of the population from where these cases are drawn, but it is possible that the population at risk may be some 20%-25% lower during these months. When allowance is made for this, the highest incidence occurs during the summer months except for the month of February, which for some reason shows a constantly high figure.

EPIDEMIOLOGY AND INFECTIVITY

The causative agent is believed to be a virus which has not been isolated. It is probable that the portal of entry is through the upper respiratory tract, though ectopic entry through wounds may rarely occur. Unlike homologous serum jaundice it does not appear to be transmitted by blood transfusion. Attempts to transmit the virus to man or animals have not been very successful.

TABLE I.—ZYMOTIC INFECTIONS 1952–1953

	3rd Quarter 1952				4th Quarter 1952				1st Quarter 1953				2nd Quarter 1953				3rd Quarter 1953				4th Quarter 1953			
	Home Shore	Home Fleet	Abroad	Total	Home Shore	Home Fleet	Abroad	Total	Home Shore	Abroad	Home Fleet	Total	Home Shore	Home Fleet	Abroad	Total	Home Shore	Home Fleet	Abroad	Total	Home Shore	Home Fleet	Abroad	Total
Diphtheria:																								
Male	—	—	—	—	1	—	1	2	—	—	—	—	—	—	2	2	—	—	—	—	—	—	—	—
Female	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pertussis:																								
Male	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	1	1	—	2
Female	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Measles:																								
Male	4	3	1	8	—	—	—	—	6	5	1	12	21	6	2	29	1	—	—	1	—	—	—	—
Female	—	—	—	—	—	—	—	—	3	—	—	3	3	—	—	3	—	—	—	—	—	—	—	—
Rubella:																								
Male	42	23	1	66	21	4	—	25	53	5	—	58	245	78	1	324	58	11	3	72	6	5	—	11
Female	7	—	—	7	2	—	—	2	5	—	—	5	32	—	—	32	4	—	—	4	1	—	—	1
Glandular fever:																								
Male	22	17	5	44	13	7	12	32	37	12	12	61	47	15	5	67	21	11	7	39	29	14	13	56
Female	5	—	—	5	6	—	1	7	8	—	—	8	3	—	—	3	5	—	—	5	6	—	—	6

Strength at		Home Shore	Home Fleet	Abroad	Total
June 1952	M	65,212	43,766	32,264	141,242
	F	4,467	—	230	4,697
December 1952	M	64,531	46,867	29,566	140,964
	F	4,684	—	293	4,977
June 1953	M	63,477	44,856	30,513	138,846
	F	4,572	—	350	4,922
December 1953	M	65,249	40,808	28,396	134,453
	F	4,443	—	363	4,806

Rates per 1,000 Total		3 Qr. 1952	4 Qr. 1952	1 Qr. 1953	2 Qr. 1953	3 Qr. 1953	4 Qr. 1953
Rubella	M	0·47	0·18	0·41	2·3	0·52	0·08
	F	1·5	0·4	1·0	6·4	0·8	0·2
Glandular fever	M	0·31	0·25	0·43	0·48	0·28	0·42
	F	1·1	1·4	1·6	0·6	1·0	1·2

Evans (1947) used 17 male volunteers aged 19–25 from an establishment where no glandular fever had occurred during the previous year and who had no history of the disease. He used unfiltered throat washings, serum and citrated whole blood and a careful check was kept, but in no instance did a subject develop the disease though 4 showed slightly suggestive symptoms, pharyngitis, lymphadenopathy and lymphocytosis, but the transient nature of these signs and symptoms and the absence of other supporting evidence make their occurrence only remotely suggestive of the transmission of infectious mononucleosis.

Taken by and large, then, transmission experiments fail, and it is clear clinically that the degree of infectivity is very slight. It is quite exceptional for members of the household or close contacts to contract the disease.

In the present series nothing approaching an epidemic occurred in any ship or establishment, the admissions being entirely random and roughly proportional to the personnel carried. The only characteristic the figures show is some tendency to rise with the years (Table II).

TABLE II

	Chatham	Portsmouth	Plymouth	Total
1948	11	22	14	47
1949	17	25	20	62
1950	7	35	23	65
1951	6	45	14	65
1952	17	47	16	80
1953	13	45	35	93
	71	219	122	412

TABLE III

Year	Anginose	Febrile
1948	28	13
1949	31	21
1950	40	18
1951	44	11
1952	41	22
1953	53	20
	237	105

The Service population of each port is fairly static over the years and one must conclude that the disease is becoming commoner amongst this particular age group. It is unlikely to be due to better diagnosis, for the condition has been widely known for the past twenty years, there are no notable recent advances in its diagnosis, and the cases represent the work of numerous different Medical Officers. Nor is it due to an increased appreciation of the part played by glandular fever in cases of jaundice or with neurological signs, for these are fairly evenly distributed through the years under review. It is generally believed that the disease now occurs more sporadically and less in epidemics than formerly. The condition started as a sore throat and cervical adenitis in children, but in 1930 there was a widespread epidemic in England characterized by its severity, duration and the high percentage of adults affected (Tidy, 1931). Since that time the disease has become commoner and more widespread, or at least much more frequently diagnosed, with a mild tendency to become epidemic. In this series no one type predominated in any given year. The yearly incidence of the anginose and febrile cases is shown in Table III, above.

Throughout the years, with minor variations, the anginose cases remained about twice as common as the febrile group.

There have been many hints that evidence of subclinical infection is common in close contacts. Halcrow *et al.* (1943) investigated an outbreak in an E.M.S. hospital in Scotland and examined 298 people, both patients and staff. Of these 97·9% had evidence of the disease, but of these only 125 had signs and 165 had suggestive blood or serological tests but no clinical signs. Many cases were shown to exist in the near-by town and other towns farther away.

Wechsler *et al.* (1946) state that during the height of the epidemic almost every patient in hospital showed a varying percentage of abnormal lymphocytes in the smears.

In the present series one is handicapped by the fact that the disease never took on an epidemic form, and both the foregoing accounts deal with epidemics. The problem then arose as to whether it was possible to demonstrate any rise and fall in the mononuclear cells of the Service population corresponding with the frequency of admission. For this purpose the three years 1951–1953 inclusive at Portsmouth have been chosen as they contain the largest number of admissions. The laboratory at the Royal Naval Hospital, Haslar, serves the Portsmouth area and averages about 300 blood counts a month, the majority being patients in the hospital and a small proportion are cases referred from outside ships and establishments. The percentage of their blood counts showing a mononucleosis of over 50% for each month of these three years has been worked out after discarding cases of blood disease and glandular fever (Table IV), the figures in brackets being the admissions of glandular fever to the hospital during that month.

TABLE IV.—PERCENTAGE OF BLOOD COUNTS SHOWING A MONONUCLEOSIS OF OVER 50%

Month	Year 1951 %	Year 1952 %	Year 1953 %	Month	Year 1951 %	Year 1952 %	Year 1953 %
January ..	5·5 (3)	2 (3)	4 (1)	July	4 (7)	12·5 (7)	6 (3)
February ..	2 (5)	7 (2)	4 (7)	August ..	3·5 (1)	11 (5)	3 (4)
March	5·0 (2)	5 (3)	2 (7)	September ..	2 (4)	9 (5)	2 (6)
April	3·5 (4)	6·5 (3)	4·5 (2)	October ..	3 (3)	4·5 (5)	5 (5)
May	7 (5)	7 (5)	4·5 (1)	November ..	5 (2)	4 (3)	9 (1)
June	4 (8)	12 (4)	8·5 (6)	December ..	2 (1)	3·5 (2)	2 (2)

TABLE I.—ZYMOTIC INFECTIONS 1952–1953

	3rd Quarter 1952				4th Quarter 1952				1st Quarter 1953				2nd Quarter 1953				3rd Quarter 1953				4th Quarter 1953			
	Home Shore	Home Fleet	Abroad	Total	Home Shore	Home Fleet	Abroad	Total	Home Shore	Abroad	Home Fleet	Total	Home Shore	Home Fleet	Abroad	Total	Home Shore	Home Fleet	Abroad	Total	Home Shore	Home Fleet	Abroad	Total
Diphtheria:																								
Male	—	—	—	—	1	—	1	2	—	—	—	—	—	—	2	2	—	—	—	—	—	—	—	—
Female	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pertussis:																								
Male	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	1	1	—	2
Female	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Measles:																								
Male	4	3	1	8	—	—	—	—	6	5	1	12	21	6	2	29	1	—	—	1	—	—	—	—
Female	—	—	—	—	—	—	—	—	3	—	—	3	3	—	—	3	—	—	—	—	—	—	—	—
Rubella:																								
Male	42	23	1	66	21	4	—	25	53	5	—	58	245	78	1	324	58	11	3	72	6	5	—	11
Female	7	—	—	7	2	—	—	2	5	—	—	5	32	—	—	32	4	—	—	4	1	—	—	1
Glandular fever:																								
Male	22	17	5	44	13	7	12	32	37	12	12	61	47	15	5	67	21	11	7	39	29	14	13	56
Female	5	—	—	5	6	—	1	7	8	—	—	8	3	—	—	3	5	—	—	5	6	—	—	6

Strength at		Home Shore	Home Fleet	Abroad	Total
June 1952	M	65,212	43,766	32,264	141,242
	F	4,467	—	230	4,697
December 1952	M	64,531	46,867	29,566	140,964
	F	4,684	—	293	4,977
June 1953	M	63,477	44,856	30,513	138,846
	F	4,572	—	350	4,922
December 1953	M	65,249	40,808	28,396	134,453
	F	4,443	—	363	4,806

Rates per 1,000 Total		3 Qr. 1952	4 Qr. 1952	1 Qr. 1953	2 Qr. 1953	3 Qr. 1953	4 Qr. 1953
Rubella	M	0·47	0·18	0·41	2·3	0·52	0·08
	F	1·5	0·4	1·0	6·4	0·8	0·2
Glandular fever	M	0·31	0·25	0·43	0·48	0·28	0·42
	F	1·1	1·4	1·6	0·6	1·0	1·2

Evans (1947) used 17 male volunteers aged 19–25 from an establishment where no glandular fever had occurred during the previous year and who had no history of the disease. He used unfiltered throat washings, serum and citrated whole blood and a careful check was kept, but in no instance did a subject develop the disease though 4 showed slightly suggestive symptoms, pharyngitis, lymphadenopathy and lymphocytosis, but the transient nature of these signs and symptoms and the absence of other supporting evidence make their occurrence only remotely suggestive of the transmission of infectious mononucleosis.

Taken by and large, then, transmission experiments fail, and it is clear clinically that the degree of infectivity is very slight. It is quite exceptional for members of the household or close contacts to contract the disease.

In the present series nothing approaching an epidemic occurred in any ship or establishment, the admissions being entirely random and roughly proportional to the personnel carried. The only characteristic the figures show is some tendency to rise with the years (Table II).

TABLE II

	Chatham	Portsmouth	Plymouth	Total
1948	11	22	14	47
1949	17	25	20	62
1950	7	35	23	65
1951	6	45	14	65
1952	17	47	16	80
1953	13	45	35	93
	71	219	122	412

TABLE III

Year	Anginose	Febrile
1948	28	13
1949	31	21
1950	40	18
1951	44	11
1952	41	22
1953	53	20
	237	105

The Service population of each port is fairly static over the years and one must conclude that the disease is becoming commoner amongst this particular age group. It is unlikely to be due to better diagnosis, for the condition has been widely known for the past twenty years, there are no notable recent advances in its diagnosis, and the cases represent the work of numerous different Medical Officers. Nor is it due to an increased appreciation of the part played by glandular fever in cases of jaundice or with neurological signs, for these are fairly evenly distributed through the years under review. It is generally believed that the disease now occurs more sporadically and less in epidemics than formerly. The condition started as a sore throat and cervical adenitis in children, but in 1930 there was a widespread epidemic in England characterized by its severity, duration and the high percentage of adults affected (Tidy, 1931). Since that time the disease has become commoner and more widespread, or at least much more frequently diagnosed, with a mild tendency to become epidemic. In this series no one type predominated in any given year. The yearly incidence of the anginose and febrile cases is shown in Table III, above.

Throughout the years, with minor variations, the anginose cases remained about twice as common as the febrile group.

There have been many hints that evidence of subclinical infection is common in close contacts. Halcrow *et al.* (1943) investigated an outbreak in an E.M.S. hospital in Scotland and examined 298 people, both patients and staff. Of these 97·9% had evidence of the disease, but of these only 125 had signs and 165 had suggestive blood or serological tests but no clinical signs. Many cases were shown to exist in the near-by town and other towns farther away.

Wechsler *et al.* (1946) state that during the height of the epidemic almost every patient in hospital showed a varying percentage of abnormal lymphocytes in the smears.

In the present series one is handicapped by the fact that the disease never took on an epidemic form, and both the foregoing accounts deal with epidemics. The problem then arose as to whether it was possible to demonstrate any rise and fall in the mononuclear cells of the Service population corresponding with the frequency of admission. For this purpose the three years 1951–1953 inclusive at Portsmouth have been chosen as they contain the largest number of admissions. The laboratory at the Royal Naval Hospital, Haslar, serves the Portsmouth area and averages about 300 blood counts a month, the majority being patients in the hospital and a small proportion are cases referred from outside ships and establishments. The percentage of their blood counts showing a mononucleosis of over 50% for each month of these three years has been worked out after discarding cases of blood disease and glandular fever (Table IV), the figures in brackets being the admissions of glandular fever to the hospital during that month.

TABLE IV.—PERCENTAGE OF BLOOD COUNTS SHOWING A MONONUCLEOSIS OF OVER 50%

Month	Year 1951 %		Year 1952 %		Year 1953 %		Month	Year 1951 %		Year 1952 %		Year 1953 %	
January	5·5	(3)	2	(3)	4	(1)	July	4	(7)	12·5	(7)	6	(3)
February	2	(5)	7	(2)	4	(7)	August	3·5	(1)	11	(5)	3	(4)
March	5·0	(2)	5	(3)	2	(7)	September	2	(4)	9	(5)	2	(6)
April	3·5	(4)	6·5	(3)	4·5	(2)	October	3	(3)	4·5	(5)	5	(5)
May	7	(5)	7	(5)	4·5	(1)	November	5	(2)	4	(3)	9	(1)
June	4	(8)	12	(4)	8·5	(6)	December	2	(1)	3·5	(2)	2	(2)

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It was hoped that by studying the blood counts for each month done on a random selection of probable contacts that some correlation with the incidence of the disease might be shown, but it is obvious that there is none. This may be due to the disease not having acquired epidemic proportions, and the number of admissions per month being too small to be reflected in the population at risk, and in most cases the degree of contact was probably remote.

Between 2% and 12% of the blood counts show a relative lymphocytosis, probably explained by the fact that the hospital population includes many cases of viral infection, colds, influenza, virus chest diseases, infective hepatitis and the like which may give a lymphocytosis. This may account in part for the higher percentages obtained in the first six months of the year and would tend to swamp smaller fluctuations carried by glandular fever.

The low rate of infectivity is also shown in the small number of medical personnel involved. There are no Medical Officers or Nursing Sisters in the present series, and only 18 members of the Sick Berth Staff and 3 V.A.D. nursing members, but 5 of the Sick Berth Staff were probationers having little or no contact with patients.

Pathology.—In most virus infections the disease process is much more widespread than was originally thought. For example poliomyelitis used to be regarded as a strictly neurotropic infection, but an initial viræmic phase appears to take place in most viral illnesses, and may involve most of the organs of the body. The same is true of glandular fever, where not only the hæmopoietic system is affected, but the nervous system, liver, skin, eyes and many other systems (*see* Symptomatology). No biopsy material from lymph nodes, liver, spleen or other tissue is available from this series of patients, but the main pathological facts are well known (Gall and Stout, 1940).

The blood picture.—This is characteristic and important. All the hæmopoietic tissues are involved, myeloid, monocytic and lymphoid, but at different times and to different degrees and can be best studied in the severe febrile illness. Firstly the myeloid system is involved, but less constantly or severely than the others; in mild cases this response may be absent though it is often marked in severe illness. During this invasive stage the polymorphonuclear count may rise to 80% of a total white cell count of 30,000 (Whitby and Britton, 1950) and the difficulty in diagnosis is obvious. This rise in the granulocytes is usually transient, but on rare occasions they may continue to rise until the fever subsides (Wintrobe, 1946). Occasionally a leucopenia and granulopenia are present at the onset.

The next stage is that of monocytic reaction which gives rise to a lymphocytosis with mononuclear cells forming 40% to 80% or more of the total white cell count; occasionally this is delayed for a week or two during which time the blood picture may be normal, but mononuclears usually begin about the fourth day and reach their peak about the beginning of the second week.

An increase in lymphocytes occurs about this time, but the monocytes settle first leaving a pure lymphocytosis.

It will thus be seen that the blood picture is a very variable one, and as Tidy (1950) remarks "no single blood picture is exclusively typical of the disease".

There are three types of mononuclear cells: ordinary lymphocytes, ordinary monocytes and abnormal cells, and the mononucleosis is mainly due to an increase in the last. The abnormal lymphocytes are not specific for glandular fever, they may occur in other virus infections such as infective hepatitis, virus pneumonia, rubella, herpes or influenza, but they are found much more frequently in infectious mononucleosis than in any other condition. They vary considerably in size and shape, and have an oval or horseshoe-shaped nucleus with a bluish-grey cytoplasm which may contain azure granules, and may be regarded as primitive non-invasive monocytes. The total white cell count may be low, normal or high, the increase is due to mononuclear cells, and the height is roughly parallel to the fever. The blood usually returns to normal within three months, but may remain abnormal for as long as ten months. In the case histories the differential white cell count is divided into polymorphonuclear cells (P) and lymphocytes (L), under which heading monocytes and glandular fever cells are included.

The granulocytes are usually but little affected; in only 3 cases in this series were they markedly reduced.

The total white cell count in this series was judged by the highest count taken during the first week of the illness (Table V):

TABLE V

Total W.B.C.	Cases	Total W.B.C.	Cases	Total W.B.C.	Cases	Total W.B.C.	Cases
3,000– 4,000 ..	6	10,000–11,000 ..	38	16,000–17,000 ..	14	25,000–26,000 ..	4
4,000– 5,000 ..	18	11,000–12,000 ..	26	17,000–18,000 ..	14	26,000–27,000 ..	2
5,000– 6,000 ..	24	12,000–13,000 ..	27	18,000–19,000 ..	5	28,000–29,000 ..	1
6,000– 7,000 ..	42	13,000–14,000 ..	22	19,000–20,000 ..	6	36,000–37,000 ..	1
7,000– 8,000 ..	44	14,000–15,000 ..	26	20,000–21,000 ..	6	40,000–41,000 ..	1
8,000– 9,000 ..	35	15,000–16,000 ..	14	23,000–24,000 ..	1		
9,000–10,000 ..	35					Total	412

The majority fall between 5,000 and 11,000; that is, the total count is usually but little raised.

On the whole, in this series, the white cell count was lower in the first week, tending to rise in the second or sometimes in the third week, but it depended largely on the severity of disease and the pattern was very variable. The 2 very high white cell counts are unusual, both were angiose cases with cervical glandular enlargement.

Eosinophilia.—Kaufman (1950) was struck by its frequency during the acute stage; of his 82 patients 22 had an eosinophilia of over 5%.

In the present series an eosinophilia of over 5% occurred in 11 patients, 4 of them within forty-eight hours of admission and the remainder on the 5th, 10th (2 cases), 12th, 14th, 21st, and 35th days respectively.

Eosinophilia during the latter stages of the illness and during convalescence is not uncommon in many acute infections and may be an expression of adrenocortical fatigue. The red blood cells were altered very little. The occasional patient showed some degree of anæmia during convalescence, the only case showing an appreciable early anæmia being the Wren with an early purpuric rash mentioned later. Glandular fever contrasts with leukæmia in this respect.

In the few cases in which they were done the platelets, bleeding and clotting time were little altered. The blood sedimentation rate seemed surprisingly little raised, though there were a few exceptions amongst the severely ulcerated throats.

In the present series of 412 cases the Paul-Bunnell was positive (1 : 64 or over) in 356. It was under 1 : 64 in 30 cases, but in 12 of these the reaction was either 1 : 28 or 1 : 56 suggesting that the reaction might have become positive if done later. In the remaining 26 cases the test was not performed.

In about 70% of cases the test was done during the first ten days and was often not repeated partly owing to the certainty with which the diagnosis could be made on clinical and hæmatological grounds, and partly to spare the patient repeated venepuncture and the laboratory staff unnecessary work.

Wassermann reaction.—The percentage of positive results is very variable: Halcrow *et al.* (1943) report none, Bernstein (1940) found it in 18% and Tidy (1934) in 50%. It is usually weak and transient, though Whitby and Britton (1950) report a case where it persisted for nine months in parallel with a positive Paul-Bunnell.

The results probably depend upon the frequency of tests, but it is noticeable that the more recent papers tend to show a lower percentage, perhaps due to the greater sensitivity of the tests and the more accurate reading of anomalous results.

In the present series the Wassermann reaction was done at some time in the illness in approximately 35% and of these 5 gave a positive result as follows:

(1) Ord. Sea., aged 19.	W.R. + 1 and P.P.R. negative on the 9th day. W.R. later negative.
(2) Sto., aged 19.	W.R. + 1 and P.P.R. negative on 5th day and 20th day. 30th day W.R. doubtful. P.P.R. negative. 35th day both negative. This patient had a past history of gonorrhœa but no syphilis.
(3) R.P.O., aged 30.	W.R. + 1 on 3rd day: later negative and Kahn negative.
(4) L/Sea.	W.R. + 2 on 4th day: 17th day W.R. and Kahn negative. 31st day W.R. and Kahn negative. This patient had had seronegative syphilis eight years before.
(5) Boy, aged 16.	Macular rash, W.R. + 1 on the 3rd day, negative later.

No real confusion with syphilis arose in any case and a positive reaction was only of academic importance, but it is of interest to note that the only patient giving more than a one plus positive had a previous infection of syphilis.

Symptomatology

Syphilis used to be described as the great imitator, and later malaria was also afforded this title. The list has grown further, periarteritis nodosa, glandular fever and several others have been included under this heading, but they all have this in common, that the disease process is a widespread one, most systems of the body are affected but one may predominate, and consequently the symptomatology is varied and diverse.

In glandular fever not only may different systems be affected, but the severity of the disease varies within wide limits.

Tidy (1950) describes the clinical manifestation under three main headings: the juvenile and adolescent types, the anginose type and the prolonged febrile types.

In the present series the degree of overlap of symptoms was such that it was often impossible to put cases into watertight compartments, and it would seem best to study them under their various symptoms.

The incubation period is usually given between five and fifteen days. Only 3 cases in the present series gave a possible story of contact, and probably none of them are helpful: 1 patient slept next to a case five weeks beforehand, another patient's girl friend is said to have had the disease four months previously, whilst the third said his child had been ill with an ulcerated mouth eighteen days before his symptoms began.

Prodromal symptoms were very common, in many cases the illness had a slow onset extending back for up to three weeks. 7 cases gave a history of tonsillitis from one to four weeks before; whether this represents an invasive phase of the disease and the main illness a recrudescence is problematical. In 1 case the attack came on fourteen days after tonsillectomy. Headache was a common prodromal symptom, 1 patient had had an increasing headache for ten days before he reported sick, a mild and variable head pain for some days beforehand occurred frequently. Malaise, asthenia and easy fatigability came next, followed by sore throat. A story of sweating at night for a few days prior to entry was common. One got the impression that the onset was usually more abrupt in febrile and angiose groups than in the glandular and abdominal types.

Sore throat.—This was the commonest symptom, it being the leading complaint in 237 (51 %) of the cases. All types were met with varying from mild faucial injection which was seldom absent to extensive involvement of the fauces, uvula and tonsils by œdema, ulceration, sloughs and membrane formation.

Faucial injection and mild hyperæmia were very frequent but might not be complained of unless the patient was directly questioned.

Next in frequency comes follicular tonsillitis, indeed this was the commonest single diagnosis on admission to hospital and there might be little to distinguish the case from the usual run of streptococcal follicular tonsillitis. They mostly lasted about five to ten days, it was unusual to get them persisting after this time.

Sloughs, ulcerated throats and membrane formations, though less numerous than tonsillitis, were far more striking and accounted for all the really filthy throats which were seen. Here again all degrees were met, occasionally there would be only a shallow ulcer on one tonsil, or ulceration might be extensive. Healing was slower than in those with follicular tonsillitis. The membrane may look exactly like diphtheria, and in fact antidiphtheritic serum was given in 5 cases. In one of my own cases, that of a midshipman aged 20, extensive greyish-white membrane covered both fauces and tonsils and stripped with difficulty leaving a raw area. The breath was foul and cervical adenitis marked and tender and it was not till the blood count was done and two throat swabs had been reported negative for diphtheria that treatment by serum was abandoned. It has been said that they lack the toxicity of diphtheria, this is probably true as none of these cases were really toxic, and the temperature is generally higher than one would expect with diphtheria.

The membrane is said never to involve the larynx, and no difficulty witn respiration was met with in the present group.

Œdema of the fauces was commonly combined with any of the above, but never gave rise to anxiety and calls for no special comment.

A generalized ulcerative stomatitis, indistinguishable from a severe aphthous stomatitis, occurred in 2 cases, in 1 case it appeared as an initial symptom four days before the onset of sore throat and malaise which caused him to go sick.

3 patients presented a picture of multiple purpuric spots in the mouth, and are worth while recording briefly.

A.B., aged 20, reported complaining of anorexia, sore throat and cough. Initial examination showed moderate enlargement of the cervical lymph glands, a palpable spleen and purpuric hæmorrhages involving the palates, fauces and inside of the cheek. His tonsils were prominent and red but without exudate. White cell count 10,800, P. 31, L. 69, and Paul-Bunnell 1 : 1,286. He developed a faint rash on the trunk and limbs three days after admission and the petechiæ slowly faded.

Marine, aged 18, reported with headache of ten days' duration and sore throat for the past twenty-four hours. T. 103° F., palpable glands in the neck and axillæ but no palpable spleen. There were numerous petechiæ on the hard and soft palate. White cell count 13,100, P. 42, L. 58, platelets 185,000. Paul-Bunnell 1 : 112.

Marine, aged 19, was admitted complaining of glands in the neck. The cervical glands were moderately enlarged but numerous petechiæ covered the fauces, buccal mucosa and hard palate. White cell count 4,600, P. 44, L. 56, Paul-Bunnell 1 : 448.

Febrile cases.—105 cases, approximately 25 %, were admitted with 'flu-like symptoms, and in this group influenza or one of its synonyms was the commonest admitting diagnosis. As a general rule sore throat, glandular swellings and splenic enlargement were not marked, but the group is a large and diffuse one, tending to merge with the others. They did, however, form diagnostic problems on admission before laboratory tests were at hand as there is little to lead one to suspect the correct diagnosis on routine examination.

2 cases will serve to show the diagnostic difficulties of the febrile cases with few physical signs.

Boy, aged 16, went sick on 8.3.51 with a day's history of malaise and shivering, but no sore throat and was thought to be influenza. There were no abnormal signs, but his temperature rose to 104° F., 105·2° F. and 102° F. on the three nights following admission. His white cell count was 10,600, P. 35, L. 65 and the Paul-Bunnell positive to 1:3,584. On the third day a few small glands were palpable in the neck and axillæ, but these were hardly in excess of normal and throughout his illness they were the only physical signs. The fever subsided slowly over a fortnight.

Sub-Lieutenant, aged 21, was admitted on 21.4.50 with a four weeks' history of occasional shivering

and, latterly, of very heavy night sweats. There were no abnormal signs, and the diagnosis of abortus fever was entertained as there was a story of being fond of fresh milk. The Widal, Melitensis and Abortus agglutinations and the blood culture were negative. His white cell count was 7,000, P. 29, L. 71, and the Paul-Bunnell positive to 1:896 (1:448 with guinea-pig kidney and negative with ox-cells). Recovery was slow but uneventful, and at no time were there any palpable glands or enlargement of the liver or spleen.

The duration of fever in all cases was very variable: on occasions it was absent, whilst other cases were characterized by a high swinging fever lasting up to twenty-four days.

Glandular enlargement.—Glandular enlargement was the leading symptom in 40 of the present series of cases, just under 10%. All degrees were met with, one case of the angiose type is described as having a "bull neck", though on the whole gross glandular enlargement was unusual. Palpable glands, thought to be pathological, were present in all but 4 cases.

The lymph nodes themselves were discrete, elastic and moderately tender though this last feature was variable. Palpable non-tender glands can often be felt in normal individuals in the neck, axillæ and groins, especially if the subject is thin and allowance must be made for this, for it is not always easy to be sure when these are pathological.

Contratto (1944) out of 196 cases says that glands were never palpable in any other region when the cervical glands were not palpable. This is not quite true of the present series where, in 2 cases with glands starting in the groin, no mention is made of cervical enlargement, and in fact a purely inguinal form has been described by Chevalliet (quoted by Bernstein, 1940).

Several cases gave a history of cervical adenopathy as a prodromal symptom extending back even weeks before the onset of other symptoms, and in a number of cases the glands only became enlarged in the week following admission. Generally speaking they were enlarged on admission and subsided in line with the fever, sometimes enlarging again if the fever rose. The cervical group was by far the most commonly affected, the two sides being about equal, followed in turn by the axillary, inguinal and epitrochlear glands.

Nolan (1935) describes a triangle of glands above the knee, the nodal triangle, which may be enlarged and tender on palpation and which when found is very suggestive of glandular fever; there is no mention of this in the present series but obviously it was not specifically sought. The glands never suppurate.

The following 3 cases presented with glands in the groin:

A Sergeant of Royal Marines went sick with a fourteen-day history of swelling in both groins; T. 99° F. W.R. and Frei were negative, and there was very little in the way of glandular enlargement elsewhere. White cell count 14,100, P. 8, L. 92, Paul-Bunnell 1 : 1,792, 1 : 896 after guinea-pig kidney absorption and negative with ox-cells.

A. B., aged 20, reported sick on 16.6.52 complaining of a swelling in both groins. He had no sore throat and no headache. He was found to have a slight temperature and to have a few inguinal glands. Two days later he had a severe rigor and his white cell count was 9,750, P. 28, L. 72, and Paul-Bunnell 1 : 896.

Stoker, aged 21, reported sick on 6.5.50. He had been struck on the shin twenty-four hours beforehand, the previous evening he had had a rigor and tender left inguinal adenitis. Examination showed an abrasion on the left shin and tender glands in the left groin. His temperature was 101° F. and his white cell count 9,350, P. 61, L. 36, M. 2, B. 1. He was treated as a septic adenitis with penicillin. However by May 12 he was still running a high swinging fever though the abrasion was healing and the inguinal glands were better, his spleen became palpable, new glands appeared in both groins and later small ones in the neck. The white cell count was now 5,400, P. 55, L. 38, M. 5, E. 2. The Paul-Bunnell was positive 1 : 896; 1 : 448 with guinea-pig kidney and negative with ox-cells. The fever finally settled after May 15 and a further Paul-Bunnell done on June 19 was positive 1 : 448; 1 : 224 with guinea-pig kidney and negative with ox-cells.

This last case is a very interesting one firstly because of the difficulty of diagnosis with the initial blood count, and secondly because of the possibility of the virus entering through an abrasion.

Anderson and Cox (1945) described a case of a physician, aged 27, who developed inguinal adenitis five days after an abrasion on the right leg. These were the only glands involved but the blood showed a 73% lymphocytosis and the Paul-Bunnell was 1:128. The incubation period is longer in this case than in ours, but it does suggest that the infecting agent may gain access through portals of entry other than the throat and respiratory tract, and although no focus was apparent in the other 2 cases presenting with inguinal adenitis, an ectopic entry of the virus cannot be excluded.

No case appears to have been described where the axillary glands alone are affected. On 2 occasions patients were picked up on routine medical inspection with lymphadenopathy and found to have glandular fever though they felt well enough to continue work.

Glandular enlargement may last a year or so (Tidy, 1937).

Splenic enlargement.—The spleen was palpable in 75 cases, or about 18%, but there is considerable variability in the figures from year to year, one hospital for one year recording a 65% enlargement rate, doubtless due to the diligence with which this symptom was sought by different Medical Officers of variable experience. The incidence is usually put at about 50%, and it is said that the spleen may be palpable when no glands are felt. Wechsler *et al.* (1946) found it in 35% of their 556 cases, but add that it would no doubt be more if persistently sought.

Enlargement is only moderate and tenderness slight and roughly parallels the lymph glands.

Abdominal symptoms.—Exclusive of jaundice, abdominal complaints occurred in 25 patients, or about 6%:

(1) Nausea and vomiting as a prodromal symptom which had been present for some days before going sick, 2 cases. One of these went on a drinking bout and had a hangover the next day with nausea and vomiting. Both these symptoms continued for three days when a sore throat appeared which caused him to go sick.

(2) Nausea and vomiting at the onset of the disease, clearing during the first week, 13 cases; this was by far the commonest occurrence.

(3) Nausea and vomiting in the second week, 1 case.

(4) Diarrhœa and vomiting 2 cases. In the majority of cases constipation was the rule.

(5) Abdominal pain 7 cases. In 4 of these it was upper abdominal, 1 generalized and in 2 in the right iliac fossa; these 2 cases were sent in as observation appendicitis and salpingitis respectively.

The cause of these symptoms is speculative, the initial nausea and vomiting suggest a toxic reaction during the viræmic stage of the illness though hepatic involvement may play its part. Early writers often mention enlarged mesenteric glands which are said at times to be palpable. Post-mortem studies are infrequent, but Dolgopol and Husson (1949) describe a fatal case with neurological complications where autopsy showed congestive mesenteric glands which were not enlarged except for those round the head of the pancreas. From the practical point of view it is important to differentiate these with abdominal pain from acute inflammatory conditions requiring operation.

Liver involvement including jaundice.—Jaundice occurred in 16 cases (about 4%) and hepatic enlargement is recorded in another 3 cases (about 0·7%).

Many of the early reports, dealing mostly with children, describe liver enlargement, and most series published since then mention it and jaundice in a small percentage of cases.

The incidence appears to be very variable, and it is a striking sign which cannot be missed so that thoroughness of examination does not play a part. In this series the incidence was fairly evenly spread: 1948—2 cases, 1949—2 cases, 1950—2 cases, 1951—3 cases, 1952—4 cases (different hospitals) and 1953—3 cases.

Without reviewing the entire literature on the subject it can be said that in at least half the cases there are abnormal liver function tests. Leibowitz (1953) found that the thymol turbidity was up at some point during the illness in 24 out of 25 cases, and he concludes that "hepatitis is an integral feature, not a complication, of most if not all cases of infectious mononucleosis". As regards these liver function tests, the colloidal gold and thymol turbidity indicate an alteration in the serum proteins, albumin and fibrinogen being made in the liver, and show a general disturbance of liver function, whilst the alkaline serum phosphatase suggests impairment of hepatic parenchyma.

The literature abounds with references to jaundice in glandular fever and as long ago as 1928 it was suggested that this was due to hepatitis and not to glandular obstruction at the portal fissure (Mason, 1928). Subsequent biopsy and post-mortem material has shown that the main lesion is a periportal hepatitis with mononuclear infiltration together with some œdema of the sinuses and swelling of the cells of the smaller bile ducts.

Leibowitz and Brody (1950) describe a case of cirrhosis following glandular fever as shown by biopsy. They followed the case through chronic hepatitis to cirrhosis in three years, the patient complaining of headaches, anorexia, indigestion and fatigue.

Leibowitz (1953) reviews the literature and comes to the conclusion that in 2,962 cases there were 144 cases of jaundice, an incidence of 4·9%.

In the present series jaundice appeared as an initial sign in 8 cases, on the second day in 3 cases, on the third day in one case, on the fourth day in 2 cases and on the fifth and eighth days in 1 case each. In only 1 case did glandular enlargement follow jaundice. In 5 cases the jaundice was trivial and transient and in only 2 could it be termed severe. In 1 case no glands were palpable.

The main difficulty lies in diagnosis and suspecting glandular fever as a cause and the following cases are recorded to illustrate these points.

Lieutenant-Commander, aged 37. This Officer went sick on 17.5.52 complaining of headache and lumps in the neck. Clinical examination showed bilateral tonsillar enlargement with exudate and marked cervical adenitis. His white cell count was 11,500, P. 28, L. 72. On May 19 general glandular enlargement was apparent and on May 21 he became jaundiced with bile in the urine. Liver function tests gave a serum alkaline phosphatase of 13 units, cadmium sulphate 3 units and serum colloidal gold 444420. The jaundice and the glands subsided during the next fortnight, but a month after admission his blood was still abnormal (W.C.C. 8,300, P. 24, L. 76). The interesting thing is that the Paul-Bunnell was done on four occasions during the course of the illness but was never higher than 1 : 14. This case was accepted as one of infectious mononucleosis, but the difficulties in diagnosis are apparent.

W.R.A.F., aged 21, went sick on 12.4.52, complaining of headache, anorexia, nausea and profuse sweating. On examination she was ill with a fever of 104° F., clean mouth but moderate cervical adenitis, congestion of the right base and a palpable liver. The white cell count was 7,600, P. 16, L. 84. Paul-Bunnell 1 : 896, and 1 : 448 after guinea-pig kidney absorption. On April 16 jaundice appeared together with a macular rash on the face, neck and trunk. The jaundice faded after three days, but this girl ran a high swinging fever for

fourteen days and a moderate pyrexia for another seven, raising the possibility of Weil's disease or other liver infection.

Seaman, aged 19, admitted 7.7.51. He gave a history of a cold in the head followed by mild digestive upset and then jaundice and pale stools. Clinically there was moderate jaundice and the liver was enlarged three fingerbreadths and slightly tender, but there were no glands. W.B.C. 10,200, P. 15, L. 85. Paul-Bunnell positive 1 : 448 (non-absorbed) and 1 : 224 (absorbed). The patient ran no fever and the jaundice cleared in a few days. This type of case is indistinguishable from infective hepatitis except by blood examination.

Lieutenant, aged 21, admitted 10.7.53. He gave a history of rheumatic fever in childhood and a day's history of malaise, heavy sweats and shivers and universal aches and pains but no sore throat and was admitted with a provisional diagnosis of rheumatic fever. On the eighth day jaundice appeared, but faded in five days. The white cell count was 18,600, P. 10, L. 90. Paul-Bunnell 1 : 1,792 unabsorbed, 1 : 896 absorbed. On July 15, five days after admission the throat became sore. This progressed until by July 25 he had a very foul, sloughing throat with much membrane, œdema of the fauces and enlargement of the cervical lymph nodes. Although the larynx is said never to be involved by membrane formation the precaution was taken of having tracheotomy instruments available. This case was a very severe anginose glandular fever in which transient jaundice appeared on the eighth day.

Leading Seaman, aged 23. Admitted 9.2.53. On February 3 the patient had developed aphthous ulcers in the mouth, these slowly got worse and on February 7 a sore throat and cervical adenitis appeared, followed by nausea, vomiting and upper abdominal pain and slight jaundice. He was admitted to hospital as an infective hepatitis; the throat was inflamed but clean, there was moderate cervical adenitis, marked puffiness of the eyes and a liver palpable three fingerbreadths below the costal margin. White cell count 21,100, P. 11, L. 89. Paul-Bunnell 1 : 896. Serum bilirubin 8 mg.%. W.R. negative. The urine contained bile until February 17, by which time the jaundice had cleared. Fever lasted for two days. This case illustrates the ulcerated mouth as a prodromal symptom and the relatively high lymphocyte count which is occasionally met with when jaundice is a complication.

The pyrexial jaundice raises many diagnostic problems on admission, but the degree of fever seems to depend mostly on the throat, where anginal symptoms are minimal the temperature is near normal and all pyrexial cases in this series had faucial involvement.

The jaundice was never severe and it would seem that in glandular fever the gastro-intestinal symptoms are less and the icterus milder than is usual in infective hepatitis.

Sporadic liver function tests done in the majority of these cases support the view that the jaundice is due to a diffuse hepatitis and obstruction of the bile capillaries. There is no evidence that obstruction by glands ever plays a part.

Rashes.—Skin rashes were recorded in 34 cases, or about 8%, and were made up as follows:

Erythematous	3 cases	Papular	2 cases
Maculo-erythematous	2 cases	Papulo-vesicular	1 case
Macular and morbilliform	18 cases	Urticarial	3 cases
Maculo-papular	2 cases	Type not stated	1 case

To this must be added one girl aged 19 who had a macular rash on admission and developed petechial hæmorrhages on the ankles, arms and neck on the third day, and another patient who had a macular rash on admission but this faded within a few hours to be followed by a fine erythematous rash on the seventh day.

Excluding these 2 cases the date of onset was:

(1) Present on admission to hospital	16 cases
(2) Appeared on 2nd day	9 cases
(3) 3rd and 4th days	One case each
(4) 7th day	2 cases
(5) 8th, 12th, and 17th days	One case each

By far the greatest difficulty is excluding drug rashes. In this respect the patient who developed a rash on the seventeenth day had been treated at the onset of his illness with chloramphenicol, and the one whose rash appeared on the twelfth day had had sulphonamides a week before. It may well be, therefore, that the incidence of recorded rashes is set rather high for in practice generally sulphonamides and antibiotics are freely given for septic throats and febrile illnesses. It will be seen that by far the commonest combination was a morbilliform or macular rash appearing as one of the initial symptoms, and the likeness to rubella was at times very close. The rashes seldom lasted for more than a few days and were often gone by the next morning. The incidence of rash seems to bear no relationship to the severity of the disease.

The distribution of the rash was most commonly on the torso and proximal parts of the limbs, the face was involved in 6 cases, alone in 1 case.

In this series the incidence of rashes was fairly evenly distributed over the years, but judging from the literature the frequency seems to be very variable; in the London Epidemic of 1930 almost all had rashes, (Tidy, 1934). Herpes has not been included in this group as it is not specific to the illness. 2 cases had labial herpes, and one case penile herpes two days before the onset of other symptoms.

Chest involvement.—Cough, usually mild, was common. 11 cases, or about 2·7%, are recorded as having signs, those of bronchitis—universal rhonchi and scattered moist sounds – in 5 cases, pain in the chest with localized pleural rub in 3 cases, bronchopneumonia in 2 cases and right basal pneumonia in one case. The months of admission were as follows:

January	1 case	September	2 cases
February	1 case	October	3 cases
March	2 cases	December	1 case
June	1 case		

in other words they were more frequent during the winter.

The blood picture did not alter greatly except in the case with a right basal pneumonia; he was admitted with a white cell count of 12,800 with 84% polymorphs, and it was the splenic enlargement which first attracted attention to the underlying pathology.

The radiological picture conformed to what might be expected—an accentuation of the broncho-vascular pattern in the bronchitics, and patchy consolidation in the bronchopneumonics, and in only one case was glandular enlargement queried and it would seem that it plays no part in these lung conditions.

In none of these cases were pulmonary symptoms severe, and they mostly cleared within a few days.

The heart.—In only one case in the present series was the heart queried, this patient had a transient apical systolic murmur and the electrocardiogram is reported as normal.

In most cases the pulse-rate paralleled the temperature, but a relative bradycardia was common during convalescence. A variety of abnormalities have from time to time been noted in the past, mostly ECG changes, alterations in rhythm, transient murmurs and the occasional friction rub.

There are several post-mortem accounts showing mononuclear infiltration of the myocardium, and it seems fair to summarize the position by saying that the heart is probably affected to a slight degree in many cases during the acute stage of the illness, but that the working capacity of the organ is unimpaired and full recovery occurs.

The nervous system.—The neurological manifestations of infectious mononucleosis are uncommon but very varied and have attracted a good deal of attention. The incidence varies from 5% to under 1% in different series.

Headache was extremely common and usually mild, and is probably toxic or vascular in origin and combined with apathy, irritability, vertigo and somnolence. It was usually frontal and far commoner in the early stages of the illness.

One case became disorientated, a boy of 15 who was admitted on 1.7.51, complaining of a sore throat and swollen neck. His throat was very foul with marked cervical adenitis, a few glands in the axillæ and groins, and the tip of the spleen was just palpable. White cell count 8,800, P. 23, L. 77. Paul-Bunnell 1:112. On July 5 he became rambling, disorientated and incontinent, a situation which lasted for forty-eight hours.

Some degree of neck stiffness was common but seems to have been more often due to adenitis than meningeal involvement, no case really simulated meningitis and no case of serous meningitis occurred in this series.

3 cases (or about 0·7%) in this series gave clear-cut evidence of nervous involvement and are worth while recording briefly.

Seaman, aged 19. First went sick on 4.1.48, complaining of aching eyes, malaise, and photophobia. He had a temperature of 104° F., slight neck rigidity, exudate on the right tonsil, conjunctival injection and enlargement of the cervical, occipital, axillary and epitrochlear glands. A streptococcus (Lancefield group A) was isolated from the throat. White cell count 10,000, P. 40, L. 60. Paul-Bunnell 1 : 448. The meningism cleared but the throat became much worse over the next five days. On January 11 pain and aching were noticed in the right arm and shoulder and on January 19 weakness of the right deltoid and serratus magnus became apparent together with an area of blunting to pin-prick over the vault of the right axilla and the adjacent part of the chest wall. This gradually improved and the patient was finally discharged on April 6, 1948, with almost complete recovery of the shoulder.

A localized neuritis of the shoulder girdle has been described during the course of a variety of maladies (Spillane, 1943), and it may well be argued that there is no evidence of the glandular fever being specifically responsible in this case.

Female, aged 28, was admitted to hospital on February 10, 1952, with the following history:

On 26.1.52 she developed a dull, generalized headache which became steadily worse, and two days later had a mild shivering attack followed by a feeling of fever. After this she improved and the headache went, but on 31.1.52 she began to feel weak on her legs, this progressed and five days later there was weakness in the arms but no paræsthesiæ, diplopia or sore throat. On admission there was a symmetrical flaccid paralysis of all four limbs, almost absolute in the legs and partial in the arms though the abdominal and spinal muscles were not affected. The abdominal reflexes and the tendon-jerks were absent in the arms and legs, the plantar responses were flexor. The white cell count was 7,950, P. 31, L. 69, and the Paul-Bunnell 1 : 896, 1 : 224 after absorption with guinea-pig kidney and negative with ox-cells. W.R. negative. C.S.F. protein 65 mg./100 ml. Globulin increased. Cells 2 lymphocytes. Lange curve no change.

By 7.3.52 some flexion of the thighs was possible though dorsiflexion of the ankles was extremely weak and the lower abdominal reflexes were returning. The upper limbs had recovered some 80% of their power. W.B.C. 6,000, P. 39, L. 61.

Recovery after this was uneventful, but it was some nine to twelve months before the patient was fully recovered.

Similar cases of acute infective polyneuritis or the Guillain-Barré syndrome have often been described in glandular fever, but it is of interest neither the glands nor the spleen were enlarged in this patient, nor was sore throat ever present.

The third case has already been reported in detail (Stride, 1953): the patient presented with an epileptic fit and was found to have cervical adenopathy and typical blood changes. Subsequent EEGs were normal.

Convulsions in glandular fever have been recorded but are rare. Bercel (1952) reported 5 cases of infectious mononucleosis showing abnormal EEG tracings, in 4 cases the picture returned to normal whilst the 5th had persistent abnormalities and later had a Jacksonian seizure.

The above cases show that the possibility of infectious mononucleosis should be borne in mind in any case of unexplained nervous disorder, even when sore throat, splenomegaly and glandular enlargement are absent. The diagnosis must rest on the blood findings and agglutination titre as the C.S.F. findings are extremely variable.

The kidneys.—The incidence of renal involvement in different series varies, Bernstein (1940) had none, Tidy and Morley (1921) had 6% of 270 cases, and Wechsler *et al.* report 3%, chiefly albuminuria, increased cellular content and hyaline and granular casts in the first week of the illness subsiding in seven to ten days. 4 of their cases had macroscopic hæmaturia.

Again the frequency is likely to vary with the diligence with which it is sought, and albuminuria during the febrile stage is probably common, but in the present series there are only 2 cases. One case had transient albuminuria during the initial stage of the illness, and cleared when the fever subsided, the other case is worth while reporting briefly.

A Shipwright, aged 23, was admitted on 13.10.53, complaining of a sore throat and glands in the neck. Examination showed considerable œdema of the uvula and fauces and well-marked cervical glandular enlargement. His urine was tested on admission and found to be normal.

On 15.10.53 his condition was worse, he complained of tightness of the chest, the cervical glands were markedly involved, the spleen was palpable and glands could be felt in the axillæ. The chest was bronchitic with rhonchi of universal distribution. X-ray of the chest showed heavy vascular markings throughout both lung fields especially in the mid and lower zones.

White cell count 12,000, P. 18, L. 82, Paul-Bunnell 1 : 3,584.

The urine contained a moderate cloud of albumin with numerous red and white cells on microscopy, but no casts.

His condition after this slowly improved, but a light cloud of albumin was still present on 24.10.53 and a trace persisted until 11.11.53.

The nephritis of glandular fever seems to carry an excellent prognosis.

Bleeding.—Various hæmorrhagic manifestations have been described from time to time, hæmaturia, rectal bleeding and hæmoptysis (Sears, 1949) and purpura (Magner and Brooks, 1942). Reference has already been made to petechiæ in the mouth.

Epistaxis occurred in 3 cases in this series, 2 of them within a day or two of admission, the 3rd on the twelfth day in hospital but whilst the throat was still swollen and œdematous when he had several severe bleedings.

There was one case of generalized purpura.

No case of rectal hæmorrhage, hæmoptysis or macroscopic hæmaturia occurred in this series.

Ocular manifestations.—Mild eye complaints such as soreness, pain on eye movement, blurring of vision and photophobia were common in the initial stages.

3 cases had definite conjunctivitis, all within the first week of the illness and all mild. One patient developed an iridocyclitis; as symptoms of the acute illness subsided he complained of sore eyes and blurred vision and developed a low-grade bilateral iridocyclitis with pigment spots in both lenses and fine, dust-like opacities in the media. He gradually improved over the next two months.

Although changes in the fundi are rare, one case had transient papillœdema.

The incidence of symptoms such as pain in the eyes and photophobia varies in different series from 1%–40%, they almost invariably occur in the early stages of the disease, are mild and are easily overlooked.

Œdema of the face.—Facial œdema, especially of the eyelids, is mentioned in 6 cases. 4 of these were anginose cases with puffiness of the eyelids during the first two days; the other 2 had only slight involvement of the throat and of the cervical glands.

Lymphatic obstruction due to glandular enlargement does not appear to be a factor as these cases show, nor does facial œdema necessarily occur in cases with marked cervical adenitis.

The œdema was never gross and subsided within a few days.

Relapses.—Recrudescences are common but all degrees of severity exist. If minor rises of fever with slight exacerbations are included, 42 cases or about 10% were affected; in only 5 cases, however, could

true relapse be said to occur and in only 1 case was there a history of a previous attack. 3 cases may be summarized for purposes of illustration.

Wren, aged 20, was admitted on 11.1.49, complaining of fever and a sore neck. Glands were palpable in the neck, axillæ and groins, but there was no splenomegaly. W.B.C. 12,700, P. 25, L. 75. Paul-Bunnell 1 : 448. Recovery was uneventful and by 29.1.49 the patient was well again.

On 18.2.49 her temperature rose again to 101°F. and the cervical and axillary glands enlarged and became tender, but settled in three days.

Marine, aged 19, admitted 30.11.51, complaining of sweating, frontal headache, sore throat and vomiting. Clinically there was general glandular enlargement but no palpable spleen. W.B.C. 13,400, P. 28, L. 72. Paul-Bunnell 1 : 256.

The fever continued for ten days and then settled, and he returned to duty on 28.12.51.

On 6.1.52 he was readmitted with a temperature of 103° F., and all glandular groups, including the epitrochlears were enlarged and tender. W.B.C. 8,000, P. 32, L. 68. On this occasion he ran a fever for sixteen days and then slowly returned to normal.

Both these cases illustrate a relapse after a short period of apparent recovery.

Sub-Lieutenant, aged 20. This patient was admitted on 20.6.49 with a provisional diagnosis of leukæmia, the Medical Officer of his establishment having examined a blood smear.

His previous history was that he had glandular fever in 1935 when aged 6, and again in 1943 when aged 14. The first was not proved hæmatologically, and he is said to have run a fever for some days and to have had enlarged glands, but on the second occasion he was at school when there was a mumps epidemic, and he went sick with lumps in his neck, had his blood examined and was labelled glandular fever.

On admission he complained of malaise, headache and lumps in the neck. The cervical glands were markedly enlarged and the inguinal and epitrochlear groups were palpable and slightly tender. W.B.C. 8,400, P. 28, L. 72. Paul-Bunnell 1 : 112 on admission.

The rest of the illness was uneventful, but the case is recorded as a probable second or even third attack of the disease.

Convalescence.—There are many references to a prolonged asthenia following glandular fever. Isaacs (1948) describes 53 out of 206 patients in whom such symptoms as ease of fatigue, exhaustion, aching of legs, weakness, depression, evening temperature, palpable spleen, low blood pressure, and low blood sugar and abnormal leucocytes in the blood persisted for a variable time afterwards, even up to four years. Children may take a long time to recover, especially their powers of concentration; Tidy (1950) has suggested this may be due to an encephalitis.

In the present series by far the most protracted convalescence occurred in the case of acute infective polyneuritis described above, where the best part of a year elapsed before full recovery was attained, but 3 other cases remained debilitated for some months afterwards. One of these cases was associated with a prolonged granulopenia, and is worthy of record.

Lieutenant, aged 24, admitted 28.10.51 as a case of tonsillitis. He had had a sore throat for a fortnight, had felt listless and tired for a week and had vomited frequently during the last three days.

Clinically he looked ill and was slightly jaundiced. Temperature 102° F., exudate present on both tonsils, enlarged cervical glands and a palpable spleen. Bile was present in the urine. W.B.C. 10,200, P. 19, L. 81 Paul-Bunnell 1 : 3,584, 1 : 1,792 with guinea-pig kidney and 1 : 112 with ox-cells.

The jaundice was slight, and this and other symptoms cleared during the next few days.

On 6.11.51 his W.B.C. was 7,800, P. 16, L. 84, and on 8.11.51 W.B.C. 6,800, P. 11, L. 89. After this daily counts were done, but on 28.12.51 his W.B.C. was 7,800, P. 35, L. 65.

He gradually returned to normal during the next three months.

On the whole, in this series dealing with healthy young adults, a prolonged convalescence was not an outstanding feature; it was the custom to grant a period of sick leave following the illness, and the great majority were fit for duty on their return.

Diagnosis

The diagnosis depends essentially on the examination of the blood, and the presence of several types of mononuclear cells, and an increase in both normal and abnormal monocytes, the rapidly changing blood picture and the absence of anæmia. All the same the initial polymorphonuclear response may cause difficulty.

Reference has already been made to vagaries of the Paul-Bunnell and Wassermann reaction. Tidy (1950) has pointed out that a very difficult diagnosis is the rare, slowly progressive chronic lymphatic leukæmia which in its early stages has periods of pyrexia with glandular swellings.

A complete differential diagnosis of glandular fever would involve a general survey of medicine, but a few comments call for special mention.

The anginose type.—Many cases are probably missed and pass off as mild sore throats, tonsillitis or Vincent's infection and can only be differentiated hæmatologically, but real difficulty may exist with diphtheria as mentioned above.

Jaundice.—Infective hepatitis may give a similar blood picture and a weakly positive Paul-Bunnell, only differentiated by absorption tests.

The febrile type may simulate undulant fever and typhoid very closely, the latter being a frequent diagnosis in the earlier epidemics.

Syphilis.—The secondary stage with fever, glandular enlargement and a rash, perhaps complicated by a false positive W.R., can be very similar.

The exanthemata.—Many of these, influenza, whooping-cough and mumps to mention a few, may have a lymphocytosis, but the most difficult is rubella, where enlarged glands and a rash complicate the picture.

The provisional diagnosis of these cases on admission to hospital represents the spot diagnosis made by the doctor who first saw the case, and covers a wide range. Several cases were first admitted to the Surgical Sections, chiefly on account of cervical or inguinal adenitis. Sore throat and its variants headed the list followed by influenza, pyrexia of unknown origin or some similar suggestion. Glandular enlargements came next, Hodgkin's disease, tuberculosis, leukæmia and, rather surprisingly, in 2 cases, hernia. Rubella was the most commonly named exanthem, though 3 cases were sent in as mumps, a malady which should not cause confusion as the salivary glands are never enlarged in glandular fever.

Prognosis.

In general the outlook is excellent, but allowance should be made for the variable duration of the illness, the possibility of relapse and prolonged convalescence. According to Lassen and Thomsen (1940) the disease may take on a malignant course and they quote a mortality of 1%–2% in over 500 cases.

Numerous fatal cases have been reported, Leibowitz (1953) has collected 38, and they mostly fall into 2 groups, splenic rupture and respiratory paralysis.

Rupture of the spleen may occur spontaneously or during straining, such as at defæcation.

Smith and Custer (1946) discuss this question and say that the capsule and trabeculæ are weakened and even broken up by cellular reaction, and that by the third week this has progressed far enough to allow rupture, and that the rate of increase in size is also a factor.

Respiratory paralysis is a risk in cases involving the nervous system, it is sometimes central and sometimes peripheral. Pulmonary complications and toxæmia account for a few cases. There were no fatal cases in this series, in fact none gave rise to real anxiety. Second infections are very rare, one possible case is recorded in this paper.

Prophylaxis.

As the degree of infectivity appears to be very low, and as the disease appears to be widespread, it is pertinent to ask what prophylactic measures should be undertaken when dealing with cases, a matter of considerable importance in the armed services where people live in Messes in close contact with each other.

Tidy (1950) states that "isolation should be carried out in accordance with the dictates of common sense for a disease which is undoubtedly infectious but only of a moderate degree of infectivity and with a favourable prognosis". There are, however, a number of factors worth considering. Very little is known of the duration of infectivity or the period of the illness when it is maximal, though it is reasonable to suppose that it is most marked in the initial stages. The anginose type, which constitutes the largest single group, may well be non-infectious and nothing is known of the infectivity in relapse.

The high incidence in the late teens and early twenties suggests that the illness mostly affects new entrants into the Service, the older age groups being immune. At the same time the steady trickle of cases from various ships and establishments suggests that the infection is universal and that symptoms appear in only a small minority of those infected. In epidemic times the virus may assume an increased virulence and rate of incidence of symptoms, but in normal times it is debatable whether anything is to be gained by isolation. There is certainly much more justification for isolating infective hepatitis.

Much must depend upon the circumstances existing at the time, but there would seem little contraindication for nursing the febrile and glandular cases in the general wards and none to so treating the anginose cases. Nervous and jaundiced cases can be treated without great risk in the medical wards where facilities for investigation and treatment are usually better.

In practice cases are seldom diagnosed before entering hospital and have a variety of titles causing them to be admitted to different sections, those labelled Hodgkin's disease, tuberculous glands of neck and lymphosarcoma, for example, find their way to the surgical wards and may need transfer, but others admitted to the general wards are best treated there, especially as a day or two commonly elapses before a positive diagnosis is made.

Treatment

No drug is known to have any effect upon the causative organism. Viruses are obligate intracellular parasites, and in contrast to the protozoal and bacterial infections, specific treatment against the viruses has been exceptionally fruitless apart from the rickettsiæ and the larger viruses of the psittacosis group.

Sulphonamides are contraindicated on account of their depressant effect upon the granulocytes. In this series they were frequently given, but usually early in the disease before the diagnosis was established, and as far as can be judged they had little effect on the subsequent white cell count.

The literature on the use of antibiotics in this condition is considerable, and all the common ones have been tried and found ineffective. Amongst our patients penicillin, Aureomycin and chloramphenicol were given at different times to different patients, without altering the course of the malady, but of these penicillin was given by far the most frequently. This subject has been fully discussed by Bennike (1951) who contrasts 99 patients treated with penicillin to 67 without it and concludes that it is hardly indicated though it may on occasions deal with secondary invaders.

An interesting experiment was tried in Denmark by Lassen and Thomsen (1940) who gave intravenous specific convalescent serum to 12 cases and reported favourable results, but the difficulties of obtaining the serum are obvious, though it may be of value in dealing with the occasional severe case in an epidemic when convalescent cases are available.

However, antibiotics are of some value in clearing pathogens from the throat and in dealing with lung complications but they are of no use in clearing the sloughs and ulcers from the throat of an uncomplicated case.

Antipyretics were commonly given, especially on the onset of the disease when the fever was at its peak. They serve no purpose, and only increase sweating and prostration.

ACTH and cortisone require special mention, for although none of our cases was treated in this way, there appear to be certain indications for their use.

Doran and Weisberger (1953) describe the use of ACTH in an 18-year-old man who was seriously ill with infectious mononucleosis—Aureomycin was given for the first five days but was without effect, and ACTH from the tenth to seventeenth day. Rapid improvement took place coincident with the use of the drug, and the authors conclude that although ACTH is not indicated for routine use in the condition, further clinical trial in severe or complicated cases is necessary to evaluate its specificity and its effectiveness.

The use of intravenous corticotrophin has also been tried in the Guillain-Barré syndrome (Blood *et al.*, 1953; Newey and Lubin, 1953) on the basis that this is an allergic reaction to a variety of different antigens. Dramatic improvement followed, but relapse occurred when the drug was discontinued but symptoms cleared again when it was re-started.

The average case, mild or of moderate severity, requires no treatment other than bed rest during the febrile stage and symptomatic treatment as the need arises. In view of the excellent prognosis no specific treatment either by antibiotics or ACTH is called for. If pathogens are isolated from the throat, or if there are chest complications antibiotics are required and the drug of choice is penicillin, other antibiotics may be needed in the case of drug resistance but it must be remembered that both sulphonamides and chloramphenicol have a depressant effect on the granulocytes. Severe cases or those complicated by the Guillain-Barré syndrome may be given ACTH with the usual precautions, but its effect in this condition has still to be evaluated.

In view of the effect upon the liver, and especially in cases complicated by enlargement of the liver or by jaundice, abstinence from alcohol and perhaps a high protein diet should be encouraged on the same lines as for cases of infective hepatitis.

The disease is frequently debilitating, and a long period of convalescence or restricted duty may be called for. Finally, where glandular enlargement has been gross it may take months to subside, but this does not mean a persistence of the disease.

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Group Captain W. P. Stamm: I doubt whether the apparent recent increase in glandular fever in adults is real. Laboratory experience shows a very great increase in awareness of the disease amongst clinicians so that many more routine requests for white counts with particular reference to glandular fever are received now than a few years ago.

In my experience Vincent's organisms are always present in the anginose type of the disease with membrane on the fauces, and this membrane can usually be distinguished from that of diphtheria by its pearly white colour.

The method of assessing the Paul-Bunnell titre is most important: some pathologists reported the original titre before addition of an equal volume of cells, while others reported the final titre. If the diagnostic titre by the first method were taken as 1/64, then the diagnostic titre by the second was 1/128.

A positive Wassermann reaction in glandular fever can often be distinguished from a true positive by the fact that the red cells are agglutinated.

Dr. B. W. Lacey: Although close contact, such as kissing, may well be the normal mode of transmission, a second possibility is suggested by Commander Rugg-Gunn's mention of a high incidence in recruits within a few months of their intake, for it recalls the similar incidence of infectious hepatitis among U.S.A. forces in Germany. I am almost certain that Dr. J. R. Paul considered that in some way this was related to the large number of injections of penicillin or prophylactic vaccines which the young Servicemen abroad usually received (Paul, 1950; Paul and Gardner, 1950). If one assumed that glandular fever was similarly associated and had an incubation period of six to eight weeks, then either social contacts or prophylactic inoculations at Christmas time might account for the unexpected peak in incidence in February.

When discussing the ætiology, Commander Rugg-Gunn did not mention toxoplasmosis as a possible cause of glandular fever, although, except for a negative Paul-Bunnell in toxoplasmosis, the two diseases may mimic each other very closely; and several cases of toxoplasmosis of glandular fever type have been described recently (Gard and Magnusson, 1951; Siim, 1951; Skipper *et al.*, 1954). It was, of course, J. O. W. Bland who first suggested the possibility because he had isolated toxoplasma in rabbits from two cases of glandular fever (Bland, 1930, 1931). His work was criticized at the time because he had not ensured that his rabbit stock was free of toxoplasmosis, but, whatever the truth is, it would appear worth while to look for toxoplasma antibodies in the serum of any case of glandular fever with a negative Paul-Bunnell test.

Commander Rugg-Gunn suggested that most authorities in this country probably regarded the glandular fever cells as abnormal monocytes, but although I have not caught up yet with the latest edition of Whitby and Britton (1953), the evidence in favour of their being of the lymphoid series seems to be very strong. To mention only one point: the glandular fever cells, like the lymphocytes, are uniformly peroxidase-negative

and show all transition forms from blast-like cells to normal lymphocytes, whereas the monocytes do not alter in appearance or number and remain weakly peroxidase-positive. A change in the peripheral blood which is seldom described, but often present and very helpful at times, is the appearance of 80–90% of stab cells with a normal number of neutrophils.

Even with proper absorptions, the performance and interpretation of the Paul-Bunnell is not always straightforward. False positives can be reported by mistaking cold heterophil agglutinins for glandular fever antibodies. In the test, the tubes are normally left standing on the bench or in the ice box overnight so that if they are not warmed up again the next morning the test may appear highly but falsely positive. Cold agglutinins often appear in trypanosomiasis (as well as in hæmolytic diseases, &c.). False negative Paul-Bunnell tests may have many origins. First there is the time factor: at the time the disease is first suspected the heterophil antibody is very often at its height and thereafter falling rapidly with the temperature and E.S.R.; a rising titre is thus the exception rather than rule (*see also* Werlin, Dolgopol and Stern, 1941; Sokal, 1943). In fact, the antibody seems to behave more like an acute-phase antibody than a normal immune one and is spread over all the globulins, rather than confined, as immune antibodies are, to γ globulins. Secondly, the antibodies may be incomplete and block or sensitize the cells without agglutinating them (Levine and Gilmore, 1945; but *see also* Eyquem and Podliachouk, 1951). In the third place, the constitution of the patient may play a part, for there is some indication that heterophil antibody is not formed in natural non-producers of Forssman antibodies (Warren, 1941). Lastly, there is the nature of the red cells used: both sheep and goats differ genetically and their cells vary widely in reactivity (Levine and Gilmore, 1945; Zarafonetis and Oster, 1950). Thus it would seem that delay in appearance of a positive Paul-Bunnell may represent only the use of more reactive cells or conversion of incomplete to complete antibody, but is probably most often due to a recrudescence of disease with a fresh antibody response.

I would entirely agree with Commander Rugg-Gunn that the smaller number of positive W.R.s found at present is mainly a reflection of improved technique. In recent times the W.R. has been made more sensitive by the use of less complement, but at the same time more reproducible by the use of preserved complement, and more specific by the use of amboceptor from rabbits intead of horses, and has been better controlled by the more general use of a flocculation test in parallel.

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Section of Psychiatry

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New Physiological Data Bearing on Problems of Consciousness

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THERE are many recent advances in clinical neurophysiology which have a direct bearing on psychiatry but also there is an increasing two-way relationship, illustrated especially by temporal lobe epilepsy. Here clinical studies have been the inspiration of animal experiments which, in turn, have led to a better understanding of this difficult field of epilepsy. Gellhorn's recent book (1953) sets the seal upon this union of clinic and laboratory.

The contribution of electroencephalography to psychiatry may be reviewed in two ways: firstly, by an assessment of recent special techniques devised to enlarge the scope of the routine EEG examination (e.g. the use of drugs such as metrazol, photic stimulation and sleep, whether natural or induced by barbiturates); secondly, by reviewing the recent advances in neurophysiology which may be related to particular problems in psychiatry or which may illuminate certain EEG techniques and observations. The first review may be confusing since no one technique has an unequivocal relationship to one clinical problem only and the physiological rationale of these techniques does not have any close connexion to current psychiatric concepts.

Three broad areas of brain function have been illuminated by laboratory study. The first is by the behavioural analysis of animals which have received lesions of selected areas of the cortex, particularly the frontal and temporo-parietal, that are considered homologous to the so-called silent areas of the human brain, which in fact turn out to be so closely related to human behaviour. The second area is the "visceral brain" (Papez, 1937; MacLean, 1949), a loose term referring to those basal and phylogenetically older parts of the cerebral cortex which appear to be intimately connected to the autonomic nervous system and the expression of emotions. Little need be said about this field since it is related to the problem of temporal lobe epilepsy discussed recently in this Section (Hill *et al.*, 1953) and still in the forefront of psychiatric thinking. The third area of the brain whose functions have been illuminated particularly by electrical techniques is the grey matter of the central regions of the mid-brain and brain-stem. It is becoming clear that the vague concepts of consciousness and unconsciousness are more intimately related to physiological function in these areas than anywhere else, and this will be discussed here.

Clinical studies have pointed to these regions for many years, for example Economo's studies of encephalitis lethargica, which led to many experiments by Ranson and others on the so-called "sleeping" and "waking" centres in the hypothalamus. Cairns (1952) reviewed the clinical evidence that lesions farther down the brain-stem also tended to produce profound disturbances of consciousness. The electro-physiological study of these areas began with Dempsey and Morison (1942), who showed that stimulation of certain areas of the thalamus produced marked alterations in the activity of the whole of the cerebral cortex. Such diffuse responses were later shown to be physiologically similar to the bilateral synchronous epileptic discharges seen in *petit mal* attacks (Jasper and Droogleever-Fortuyn, 1947). This was the first laboratory evidence for the long-standing clinical view that this type of epilepsy originated somewhere in the mid-brain region. Magoun (1950) also showed that diffuse cortical changes resulted from stimulation of areas farther down the brain-stem, which clarified the earlier observations of Bremer (1935) that the cerebral cortex of the cat exhibited the electrical patterns of sleep after division of the brain-stem. He thought this was due to the removal of all afferent influences, passing up the brain-stem in the lemnisci. Magoun's (1950) experiments showed, however, that the sleep patterns of the cerebral cortex were altered to waking patterns not by stimulation of the lemnisci systems but by stimulation of the diffuse reticular substances below the aqueduct and third ventricle. There is evidence for the existence of collaterals which are given off from the main ascending sensory tracts and go to these reticular substances (Morin and O'Leary, 1950), thus making two ways for sensory stimuli to reach the cerebral cortex, the direct lemnisci or through numerous relays in the reticular substance. The former gives a relatively discrete spatial localization of sensory stimuli in the primary cortical receiving areas with sharply localized spike-like discharges of short latency, so that special techniques are usually required to demonstrate this activity on the scalp (Dawson, 1947). Only the arrival responses to visual stimuli are of high enough amplitude to be easily picked up by routine EEG methods. The indirect system has a more diffuse excitatory influence on most of the cerebral cortex, the activity being of longer latency, of less sharp form, and variable in appearance. Moreover, the same area of reticular formation receives impulses from all sensory modalities and stimuli from different senses tend to compete (Amassian, 1952). These two systems differ in their sensitivity to drugs. French *et al.* (1953) have recently suggested that the anæsthetic state is due to a selective depression of activity in the diffuse reticular system.

As might be expected, chronic lesions of the brain-stem in the cat (Lindsley *et al.*, 1950) produce somnolence with sleep patterns in the EEG which can be only momentarily changed to arousal patterns by afferent stimulation. In monkeys (French and Magoun, 1952) the lesions have still profounder effects with irreversible coma, the largest lesions causing death. All the main electrical phenomena seen in animals have been confirmed in many laboratories, including our own. Sleep records are now frequently taken not only for the value in bringing out temporal lobe epileptic foci (Gibbs and Gibbs, 1947) but also for study of other phenomena (Lairy-Bounes and Fischgold, 1953). This is perhaps the first time that purely electro-physiological techniques have delimited a functionally discrete area. The pathways whereby the cortex is affected have been worked out by Starzl *et al.* (1951).

The status of the sleep and waking centres of the hypothalamus should be mentioned. The areas which, when stimulated, cause arousal of the cortex are without doubt of the same functional system as that just described. However, Hess (1949) has claimed that there are other areas which when stimulated cause sleep. His son (Hess *et al.*, 1953; Akert *et al.*, 1952) has recently published EEG evidence bearing on these claims. In these experiments sleep appears to come on several minutes after the electrical stimulation has stopped and the causal relationship is equivocal. Bremer (1951) comments on the difficulty of accommodating in current neurophysiological theory the idea of stimuli producing inhibitory states. It seems easier to see the problem of sleep as "How does the brain keep awake?" than "What puts it to sleep?" The only difficulty about this point of view is that it makes sleep a negative condition, whereas it is obviously one of the greatest importance for the life of the organism, for the organization of which one might expect to find special areas, especially in view of the complex somatic changes that occur outside the central nervous system.

The possible clinical correlations and behavioural changes in man associated with these animal experiments may now be discussed. Lindsley (1952) and others have produced diagrams showing the gradual change of the EEG from low-voltage fast activity to high-voltage slow waves as the subject passes from full consciousness to deep coma. This spectrum of activity seems to be related to the influence of the reticular substance on cortical rhythms. Clinical observations of abnormal EEGs and certain experiments suggest that there are various bilaterally synchronous rhythms which may be due to fractionation of activity in the reticular region. Nor is it certain that only this region can produce bilaterally synchronous discharges. For example, Wall *et al.* (1953) suggest that the pathway responsible for abnormal responses to photic stimulation involves the pre-tectal area, the activity of which system is reciprocally related to the reticular substance. Walter and Walter (1949) and Ulett and Glaser (1952) have shown that normal photic responses are modified by the patient's tension, which is clearly related to the low-voltage fast end of the spectrum of EEG activity. Numerous studies by Pampiglione (1952, 1953*a*, *b*) and others have shown that abnormal responses of epileptic type produced by photic stimulation are modified by other stimuli altering the general level of attention of the subject. The findings of Leiberman and Hoenig (1953) on recurrent catatonia may be explained similarly. The withdrawn catatonic subject whose record contains slow activity produces less abnormal photic responses than the same subject does when out of catatonia, paying more attention to the environment and having a flatter EEG.

At the lower end of this scale of awareness are the various abnormalities during the course of epileptic attacks. In their earliest paper on this subject Jasper and Droogleever-Fortuyn (1947) thought that it was likely that there were several possible patterns of influence of the reticular substance on the cortex which were probably anatomically discrete. The effects on consciousness of the 3 per second spike and wave *petit mal* attacks, which begin and end instantaneously, and the equally symmetrical slow waves of the psychomotor type of seizure are strikingly different. The EEG course of some psychomotor attacks is a slowly progressive increase in amplitude and decrease in frequency of waves from about 6 to 2 cycles per second (Hill, 1949). The same march of events can usually be discerned underneath the high voltage spike discharges found in the true major seizure. The disturbance of consciousness in the two fits is probably related to the slow-wave activity, to which in the major seizure are added the EEG spikes and the tonic-clonic muscular movements. Williams (1953) has recorded the electrical activity of the human thalamus directly and shown that spike and wave bursts of *petit mal* tend to originate here, although the precise origin of these discharges cannot be localized by this method of investigation.

He also deals with the changes that occur in a different clinical condition, i.e. stupor (akinesis and mutism) associated with epilepsy. Spindles of rhythmic activity were present in the thalamus, largely independently of discharges at the cortical level, where the routine EEGs were nearly normal. The spindles were greatly enhanced by a small dose of Pentothal, which is reminiscent of the changes seen in subacute encephalitis (Williams and Parsons-Smith, 1951). In sleep and coma there is a profounder disturbance of consciousness, clearly related to the greater EEG changes at that level.

Characteristically, however, basal disorders affect both cortices fairly symmetrically, although unilateral cortical lesions can produce asymmetrical arousal responses. Lairy-Bounes and Fischgold (1953) claim that post-central lesions are likely to show disturbances of reaction to stimuli and that this can be related to a clinical sectional disturbance of consciousness in Martin's (1949) sense (i.e.

in association with an agnosia). Fig. 1 shows the clinical usefulness of the new knowledge of arousal responses obtained from animal experiments.

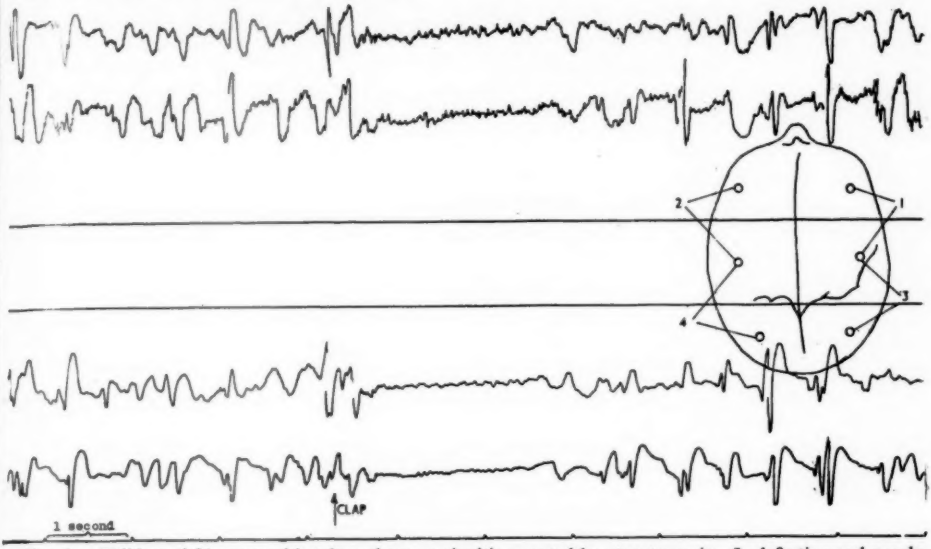

FIG. 1.—Child aged 3½ years with tuberculous meningitis arrested by streptomycin. Is defective and nearly blind and deaf. Nevertheless this EEG shows that abnormal cortical activity is arrested with the appearance of a normal flattening of alertness to a sound, in spite of there being no clinical "attention."

Bremer (1951) and Jasper have both made observations showing that the cortex does still function in some way even when apparently asleep. The well-known differential tendency of people to wake to certain noises of an unexpected variety clearly requires some discriminatory activity at the cortical level. Bremer and Terzuolo (1954) have shown that generalized arousal responses can be obtained by electrical stimulation of the cerebral cortex via the activation of the reticular formation, and moreover that destruction of the auditory cortex alters the arousal responses to auditory stimuli but not to those of olfaction or touch. Jasper *et al.* (1952) have shown by electro-physiological techniques that stimulation of many parts of the cerebral cortex can cause responses in the reticular substance so that the necessary corticofugal pathways are present. Pampiglione's (1952) studies have shown the extinction of arousal responses with the repetition of the same stimulus but a return of the arousal response with a different sensory stimulus, even if of the same modality. These results can be interpreted in straightforward Pavlovian terms. Such a discrimination certainly implies cortical activity of a sort. Learning, at a more complex level, however, would seem to be impossible and the alleged beneficial effect of sleep on retention of just learned material is probably due to the absence in sleep of distracting stimuli.

Further light on the actual role of the reticular system in consciousness may come from a study of the clinical syndromes that are said to be associated with brain-stem disorders. In addition to the gross disturbances of consciousness that result from acute lesions, there is, for example, narcolepsy. Pond (1952) has suggested that this disorder is essentially a functional lability of the sleep-waking rhythm so that normal sleep patterns are more easily produced, particularly in response either to certain stresses or to the minimal quantity of the conditions that make for drowsiness in normal people. The phenomena of sleep paralysis, sleep hallucinosis and cataplexy all appear to be a functional fractionation of the sleep-waking mechanism.

Profound disorders of memory also occur from lesions suspected to be primarily in this area. Gantt (1942) has shown that conditioned reflexes are not easily acquired by established Korsakov cases. It would appear that already acquired discriminatory responses are safe in the cortex but the learning of new material involves a general activation impossible in cases of brain-stem damage. One of the outstanding effects of epileptic attacks involving loss of consciousness is the length of the post-ictal amnesia which can often be correlated with the degree of post-ictal slowness in the EEG.

The so-called Stammhirn syndrome is characterized by excessive activity, irritability, impulsivity and erratic responsiveness, symptoms which are in contrast to those just discussed. This suggests that the capacity to sustain cortical activity at a set level of attention has become impaired so that "learning" is difficult. Bradley and Elkes (1953) have shown that amphetamine acts at this level and it is known that this drug has a marked calming influence on such cases. The calming is paradoxical

in that it results from the increased capacity of these subjects to give sustained attention to their surroundings so that their activities are more adapted to reality.

These facts bring out the complexity of functions underlying what is called consciousness. It has really been clear from the time of William James onwards that consciousness is not localizable, nor is it in any way a unitary state, but James did insist that consciousness had, or rather was, a function. We are now perhaps in a better position to see the parts played by the cortex and the basal structures in the development of the picture of full consciousness. Martin (1949), in his recent lectures, divided disturbances of consciousness into "global" and sectional. His lectures were written just prior to the identification of the activity of the reticular substance so that he was able to relate the former only to the basal regions generally and not to the diffuse reticular system. Although anatomically it seems that the direct lemnisci systems are main tracts which then give off collaterals to the reticular substance, it would seem that evolutionarily the latter system is really older and more primitive. It is rather that this system gives off collaterals so as to provide a direct pathway of discrete sensory information to the so-called higher centres. Full consciousness depends on contributions to the cortex of both parts of this system, which may vary independently. Penfield (1952) argues that the reticular region is a centre in the sense that only in this region does the activity of all areas of the cortex get mixed together, but one may disagree in thinking that this is the highest functional level. Anatomically and electrically the activity of the reticular substance is curiously primitive and diffuse. It occupies a sort of functional lower level between the greatly expanded capacities for sensory discrimination on the one side and on the other the increased motor agility which depends on the phylogenetic development of the cortex in higher animals. Nevertheless the neurophysiological facts bring out clearly that sleeping, waking and attention are stages on a continuum with an infinite gradation and variation of degrees of awareness, not an all-or-none reaction. The EEG and neurophysiological facts are still a long way from many of the most important disorders of consciousness with which psychiatry deals. The psychoanalytical concept of the unconscious for example still lacks any physiological basis. It is certainly a dynamic repression rather than a depression of function and a consideration of how this comes about would go beyond the facts and experiments reported here.

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The Electroencephalogram in Affective Disorders

By Denis Williams, D.Sc., M.D., F.R.C.P.

Although Hans Berger was a psychiatrist and made all his original observations on the patients and staff of a mental hospital, using one group as abnormals and the other as controls, in the quarter of a century that has elapsed since then, his electrocncephalogram has contributed little which is of positive value to the clinical psychiatrist. Denis Hill pointed this out in the First World Congress of Psychiatry in Paris in 1950 when he said that although every clinical syndrome of psychiatric interest had been studied, "If epilepsy and the local brain lesions are excluded, the lack of diagnostic specificity has proved disappointing" (Hill, 1952). He went on to argue, however, that as a tool in psychiatric research the EEG is very valuable.

It seemed so reasonable at the time that the EEG should immediately answer some, at least, of the multitude of psychiatric questions, since the brain is the organ of the mind. Making every allowance for the place of environmental stress in determining disorders of thought, feeling and behaviour, there remains the great contribution to the pattern of psychiatric disorder of the immutable personality based on the physical brain and body. Such disorders of thought as schizophrenia, of feeling as recurrent depression, and of behaviour as perversion, have surely at their basis a deviation from the average behaviour of the nervous system. In these people then, there would surely be some evidence of this deviation reflected in disorder of the electrical activity of the cerebral hemispheres. In consequence, therefore, large numbers of patients, in whom accurate psychiatric diagnoses were made, were subjected to the benign ordeal of electroencephalography—as easy to inflict as it was painless to suffer. It was found that some—a significant proportion—had abnormalities, but these abnormalities were inconsistent in their pattern, their site, and their relationship to the disorder under study. The facts of all these studies are found in standard texts such as that of Hill and Parr (1950), Gibbs and Gibbs (1952), and Cohn (1949). In general they showed that the incidence of easily recognized abnormality was about twice as high in chronic neurotics and in schizophrenics, and four times as high in aggressive psychopaths as in the normal population. And yet there were striking anomalies: over two-thirds of all schizophrenics, and nearly all manic-depressives, had normal EEGs.

Although electroencephalographic departments and EEG costs rose steadily in mental hospitals, their main function in most was to exclude unsuspected or suspected organic disease of the brain—to reveal the hidden tumour, or to solve the problem of the atypical epileptic. While this was happening, some workers were studying isolated cases in detail, and breaking down the large groups studied, in a search for correlates.

It would be worth while at this stage to consider why it was that so little of a positive nature emerged from a study of the routine electroencephalographic records of psychiatric patients.

First, the EEG does not record cerebral action potentials. It has not the same relationship to brain activity as has the action potential of a peripheral nerve to nervous conduction, or the electromyogram to muscular contraction. Rather, it seems to be a complex of alternating electrical potentials upon the background of which cerebral nervous conduction and integration take place. The electrical activity revealed by the amplifying and recording devices is not a direct reflection of brain function although it does reflect brain activity. There is, in consequence, no reason, even at the lowest possible level of function, to expect a direct relationship between the form of the EEG and the functional results of cerebral activity. A banal example of such an expectation was seen in the volume of work undertaken in the last war to try to establish a relationship of practical value, between the capacity to fly an aircraft efficiently in the face of enemy action, *and the will to do so*, with features in the EEG. The emphasis here is on the phrase "of practical value". Of course distant relationships, of philosophical interest, were established, but had there been a close relationship, psychiatry would have become neurology, and neurology one of the humanities.

Secondly, the EEG records, through its scalp electrodes, the combined electrical potentials of millions of differentiated cells, the electrical activity of any one of which is not yet understood. The end-result is correlated by the clinical electroencephalographer with the total end-result of the clinical syndrome. This has proved meaningless, but electrocorticography is telling us more of what is going on in discrete areas of the brain.

It seems important to establish the point that presence or absence of abnormality in general was unlikely to relate to psychiatric disorders. Detailed study of individual waves or rhythms arising in different parts of the brain, and each related to the occurrence of different wave forms or frequencies elsewhere, the modification of these isolated waves by physiological or chemical changes, and exploration of submerged cortex and deep grey matter, must be undertaken before the meaning of records is clear.

Thirdly, the recording methods we use are quite crude, in so far as they merely amplify and impress on paper what is happening to the resting brain. Activating techniques, stress situations, and a more dynamic approach to the brain in activity will yield more information, but this is going to require a potential of skill, staff and equipment beyond the range of any but highly specialized academic departments (Gastaut, 1950). Stated briefly, routine recording within the capacity of a clinical

department will offer little more to the clinical psychiatrist until there has been a great increase in knowledge of the detailed physiology of the EEG.

Fourthly, the EEG records simple physiological changes in cell activity which are not reflected in the complexity of integration of the human brain. The records from the head ganglion of insects, as Adrian found with the water beetle, are similar in many respects to those from man. They represent the electrical counterpart of alternating biochemical rhythms. Although integrated neuronal activity is ultimately dependent upon these changes, it does not directly change in response to alteration in them. A notion that it might, is inherent to the uncritical reader of such delightful books as Walter's (1953). The relationship need not necessarily be more close than the brain's dependence on other bodily changes, such as those in blood glucose or acid-base balance. It is therefore unwise to expect to see in the EEG a reflection of the capacity to think deeply or even reasonably, to experience emotions, or to engage in reasonable interpersonal relationships. It is, however, reasonable to look for reflection of some of the *causes* of disorder of these high functions, and that the search has been successful is seen in studies of psychopaths and delinquents (Levy and Kennard, 1953; Hill and Pond, 1952; Stafford-Clark and Taylor, 1949), in immature persons (Cattell and Pacella, 1950), schizophrenics (Finley and Campbell, 1941; Hill, 1948) and particularly catatonics (Hill and Rowntree, 1949).

It must be evident from the brief statement of past experience I have outlined that the *whole* EEG cannot be closely related to the *whole* psychiatric problem. There are, however, ways in which it can at present be employed to advance knowledge of the patient under study and of the basis of his disorder.

First, and obviously, to help to exclude gross organic disorder—focal or general—of the cerebral hemispheres, or to reveal though not to exclude, epileptic disturbances. It is at the heart of good medicine to expect the unexpected but to be surprised when it occurs.

Secondly, by direct recording from the brain, to study and modify local cerebral disorders related to abnormal feeling or behaviour. This method is being employed in aggressives who have demonstrable electrical lesions of the anterior part of one temporal lobe (Hill and Faulkner, 1953), and in the removal of epileptic foci in the same neighbourhood (Earle *et al.*, 1953). This involves recording below the cortex as well as upon it (Williams and Parsons-Smith, 1951).

Thirdly, by the use of activation techniques which modify the EEG and may reveal changes which are hidden in ordinary circumstances (Gastaut, 1950).

Fourthly, to relate changes in the EEG to single aspects of temperament or personality, such as arrest of maturity, seen in the immaturity of so many psychopaths (Cattell and Pacella, 1950), or evidences of aggression (Hill, 1944).

Lastly, to study in detail unusual cases where isolated psychiatric symptoms exist in association with demonstrable electrical changes, since special cases of this kind may cast some light on the hidden disturbances of cerebral physiology responsible for the whole complex psychiatric disorder. Local cerebral disturbances, or toxic states, may mimic features of schizophrenia, and their detailed study is a step in the study of schizophrenia as a disease of cerebral physiology.

I would like now to consider disorders of affect in this manner, since I have seen in neurological practice a group of people who have disturbances of feeling, loosely called psychiatric, in association with changes suggesting they are the direct result of disturbances of cerebral physiology. It is in patients with affective disorders, more than in any other psychiatric state, that the electroencephalogram is silent. Berger wrote in 1931 that he could find no certain abnormality in the electroencephalogram in manic depressives in either phase, and that has been common experience since (Gibbs, 1942). It might be expected that a group of subjects having reactive depressions to environmental stress would have characteristics in the EEG similar to those of the normal population, but it seems strange that no single characteristic of the EEG has been related to the abnormal mood swings of a cyclothymic patient. It is true that in the preoccupied, depressed or anxious person the alpha rhythm may be suppressed due to attention, with consequent evidence of the faster rhythms, but nothing else of note is seen (Cohn, 1949).

The involutional depressions are, however, accompanied by changes in the electroencephalogram. Finley (1944) found an excess of faster rhythms; Greenblatt (1944) considered that 51% of over 1 500 patients with an involutional psychosis had an abnormal electroencephalogram, in contrast to those with manic-depressive psychosis. Here then is further support for the widely accepted recognition of the fundamental difference between the involutional and the manic-depressive psychosis initially recognized by Kraepelin. Except that Finley (1944) found preponderance of fast rhythms of 15 to 20 c/s in these subjects there has been no specific electroencephalographic patterns in them, such as exists for instance in the epilepsies, and there is no knowledge at all of the neurophysiological basis of either kind of affective disorder.

I have recently studied in some detail 5 patients with severe affective disorder in a setting which suggested to me that the disturbed emotion and mood had a physical basis in disorder of cerebral function. The main clinical features of their illnesses are enumerated in Tables I and II. All were women, all married, one childless. None had had similar psychiatric illnesses, but all had been emotionally robust. The family history in none revealed any marked predilection to psychiatric disorder, but one had an epileptic son. They were all physically healthy and none had signs of neurological disease.

TABLE I

		1	2	3	4	5
Case		E. T.	K. C.	H. P.	D. F.	M. S.
Years of illness		1½	3	2	2	5
Disturbances of feeling:						
Sensations	Common	+	+	+	0	+
	Smell	+	0	0	+	0
	Taste	+	0	0	+	0
	Sight	+	+	0	0	+
	Hearing	+	+	+	+	+
Emotion	Misery	+	+	+	+	+
	Paranoid	+	+	+	+	+
	Worry	+	+	+	+	0
	Horror	+	+	0	0	+
Mood	Depression	+	+	+	+	+
Compulsive thoughts		+	+	0	0	+
Previous personality		Good	Good	Good	Good	Good
Environmental stress		+	0	+	0	++

TABLE II

	1	2	3	4	5
Case	E. T.	K. C.	H. P.	D. F.	M. S.
Convulsions	0 (son +)	+	+	0	+
Physical signs	0	0	0	0	0
Dementia	0	0	0	0	0
EEG Abnormal	+	+	+	+	+
Bilateral	+	+	+	+	+
Temporal	+	+	+	+	+
Improved	+	+	+	0	0
Therapeutic response:					
Anticonvulsants	++	++	+	0	+
E.C.T.	—	++	0	0	—

The feature common to all of them was a state of stereotyped organic hallucinations which had lasted from one and a half to five years. They all heard voices, 3 had grotesque visual hallucinations at the same time, 2 also had hallucinations of smell and taste, and all but one had disturbances of bodily feeling at the time of the hallucination. The hallucinatory state would last for minutes or hours the hallucinations were intense, horrible and realistic. During them the patients had no insight, and with them there was a complex and intensely severe emotional experience. The emotions were compounded of dread, horror, intense apprehension and misery. In all, the patients had an overwhelming experience of personal reference during the hallucinatory state. At the same time compulsive thoughts of a horrible nature were imposed on the subject. During each episode there was intense depression which persisted afterwards for hours or days. It was my belief that just as the sensations of sight, sound, smell or taste were hallucinations, so the complex disturbances of emotion and mood were also hallucinations. Lest the purist may contend that an hallucination is perception without a stimulus, the perception being presumably outside the body, may I affirm that percepts arise within the body also—where emotions and moods have their origin and experience. The narrow usage of the word "hallucination" is of recent origin, and the verb *allucinari* means "to wander in the mind". Here then were people with hallucinations of emotion and mood, for surely the subjects of feelings which arise without a stimulus have hallucinations. In the sense in which a neurologist refers to an organic hallucination, therefore the mood disorder of the manic-depressive and the involutional who is depressed without adequate cause is an organic hallucination.

In these cases very full psychometric, psychiatric and neurological study gave no evidence of a cause. 3 of the subjects had had convulsions, and so had the son of another. It may well be thought therefore that these were all bizarre epileptic states. Certainly all had abnormalities in the electroencephalogram and 4 were improved by anticonvulsants.

A brief example of one of the cases was:

A hard-working housewife of 57 years began eighteen months before to have distressing experiences. There was a sudden buzzing, then a sensation in the nose followed by an unusual unpleasant smell. There was déjà vu, and then everything appeared grotesque, revolting and sinister. Faces became distorted, and she had hallucinations of horrible faces too. With this, evil thoughts which she was unable to dispel forced themselves upon her. She had sensations of a voice whispering something unpleasant, but could not distinguish what was said. With this also there were bodily sensations of sinking and fainting but "the worst thing is the feeling of depression and the beastly thoughts which come into my mind, like a nightmare in the daytime". Dread, revulsion and horror were mingled, but when they subsided the intense depression remained. These experiences occurred frequently and only lasted a few moments.

She was studied in psychiatric hospitals and clinics and during the period under my care she was also studied by my psychiatric colleagues and there was universal agreement that her experiences were the result of an "organic" or "epileptic" state. The EEG (Fig. 1) on several occasions was abnormal and showed spike

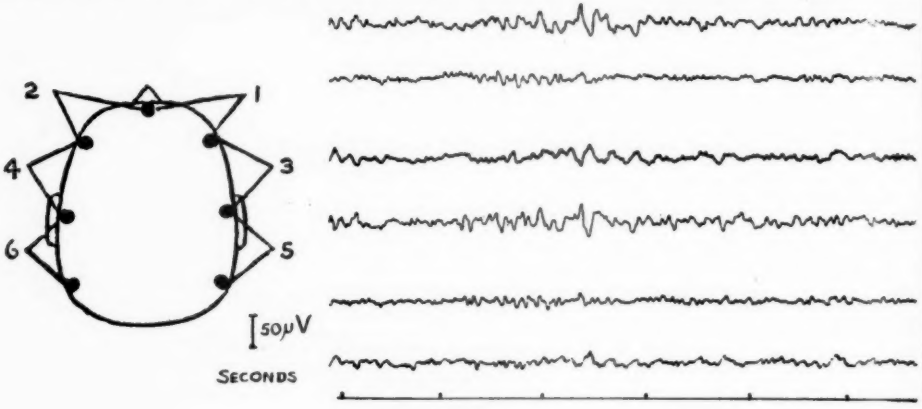

FIG. 1.

discharges in both mid-temporal areas, particularly on the left. She was studied in Netherne Hospital, Guy's Hospital, St. George's and the National Hospital. Three courses of E.C.T., 3, 7 and 8, were used with no more than a few hours' benefit. She was then given phenytoin sod. 0·1 gramme with phenobarbitone 0·05 gramme, twice a day, with relief which has persisted. She has been followed for two years and remains well. The EEG has remained abnormal. Although most subjects of affective disorders have no evident abnormality in the EEG, in this small group abnormality exists.

Cases of this sort may, in consequence, offer a little information upon the cerebral physiology of disorders of emotion and mood. Even though the epileptic experience is a caricature of the normal it does offer in the electroencephalogram a demonstrable concomitant of cerebral dysfunction. Here in subjects of mood disorder of an unusual kind the electroencephalogram shows a cerebral disturbance. Much more elaborate study with direct cortical recording and activation techniques would be needed to localize the disturbance more accurately. Similarly in the endogenous affective disorders of everyday occurrence, surely new techniques will end the silence which envelops their cerebral basis.

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Section of Neurology

President—E. A. CARMICHAEL, C.B.E., F.R.C.P.

[*March* 4, 1954]

DISCUSSION ON FACIAL PAIN

Dr. John Penman: *Some Shortcomings in the Present Treatment of Tic Douloureux* [*Abridged*]

Tic douloureux is a chronic progressive disease of unknown pathology, whose only constant feature is brief paroxysms of severe unilateral pain in the trigeminal area, with certain precipitating factors. The pain must be unilateral, trigeminal, severe, paroxysmal and precipitated. There are bilateral cases, but a patient who has already had the pain on both sides of the face, and has not yet had it radically treated on either side, is a great rarity; and even he will have had many paroxysms limited to one side. For practical diagnostic purposes, therefore, tic douloureux is strictly unilateral; and any pain said to be mainly on one side, but tending to wander a little way beyond the mid-line, belongs to some other disease.

The terms trigeminal, severe and paroxysmal are self-explanatory. There must be at least several precipitating factors; it is not enough for the pain to be brought on, say, only by movements of the jaw, only by bodily exertion, or only by cold.

These attempts at definition and description are necessary because many writers claim to cure "trigeminal neuralgia", or "major trigeminal neuralgia", without making clear what it is they are curing.

Tic douloureux, thus defined, can be satisfactorily treated by interruption of all the pain-conducting fibres in the trigeminal sensory pathway at any point between the trigeminal ganglion and the nucleus of the descending tract. It can be satisfactorily treated, but how often is it? This question falls under four heads: availability of treatment, choice of method, drawbacks of treatment, and acceptability of cure to the patient.

(1) *Availability of treatment.*—It would be pleasant if one could say that most sufferers from this disease, when they first seek medical advice about it, obtain a prompt cure, but the truth is different. Some doctors do not think of such a rare diagnosis; some think of it but will make it only by exclusion, that is, not until every disorder of teeth, nasal sinuses, eye, ear, throat and jaw has been unavailingly put right. A few, having made the diagnosis, still tell the patient that there is no cure, or deter him with stories, dating mainly from the 1890s, to the effect that operation frequently leads to death or at least to facial paralysis and loss of an eye. More than a few act on the belief that trigeminal injection, though not very useful, is not difficult either, and that every doctor should try his hand at it when occasion demands. As Cushing (1920) wrote: "There are no rules to follow. One introduces the needle to the nerve"; or as Horrax and Poppen (1935) put it: "An alcohol injection can be performed quickly in the office." Many of those who have the skill to provide a permanent cure deliberately begin with a temporary one by means of peripheral injection.

Not every patient encounters all these forms of delay, but most patients encounter several, and it is not unusual to hear of some years spent in pain and unsuccessful search for relief. We have a fully worked out symptomatology and some effective therapeutic techniques, but they are often wasted.

(2) *Choice of method.*—The essential features of a good operation are a low death rate, a low relapse rate and absence of any serious post-operative disability. Of the major trigeminal operations, undoubtedly the safest is subtemporal rhizotomy; the mortality from it in the best hands is about 0·5%, and in all hands at a good neurosurgical centre, as Grant (1938) has shown, about 2%. Suboccipital rhizotomy, so all published figures suggest, is less safe, and medullary tractotomy must by its very nature be less safe still. The relapse rate also is lowest after total subtemporal rhizotomy (about 2% according to Grant, 1938), and highest after tractotomy (37% of 124 cases at the Selimer Hospital, according to Guidetti, 1950).

All these operations are carried out only in selected cases. Frazier and Gardner (1928) wrote: "When the blood pressure is 200 or over the patient may receive an alcoholic injection", and Jefferson (1931) said: "I have arbitrarily fixed 70 years as a limit"; that is, patients over 70 years old are to be treated by injection instead of rhizotomy. We can be sure that every surgeon likes to draw the line at some similar blood pressure and some similar age.

SEPT.

But if alcohol injection is good enough for these very elderly and frail people, why is it not good enough for younger and healthier people? The usual answer is that it is always temporary in its effects, but that is quite untrue. A most important distinction must be made. On the one hand there is injection distal to the cells of the trigeminal ganglion, which is followed by regeneration of peripheral nerve fibres and by a return of sensation. On the other hand there is injection proximal to the ganglion cells, among the fibres of the pars triangularis of the sensory root. It is commonly called "ganglion injection", which is a misnomer; a better name would be alcohol rhizolysis. As the careful researches of Dr. Marion Smith have shown, this more proximal injection is capable of causing destruction of the fibres of the descending tract of the trigeminus, which have no sheaths of Schwann and therefore cannot regenerate (Penman and Smith, 1950). The interruption of the sensory pathway is lifelong.

Welcome though this histological confirmation is, it is no more than confirmation of what has been proved clinically for many years. In the very first recorded case of percutaneous alcohol injection of the trigeminal sensory root, the patient was followed up for sixteen years, at the end of which time the trigeminal area on the affected side was still anæsthetic (Taptas, 1931). If it is done with care and patience, a single injection will, in at least 90% of cases, cause lifelong sensory loss of sufficient degree to provide lifelong cure.

Since alcohol injection has virtually no death rate and can give lifelong cure, it ought surely to be tried first in all cases, except those few in which preliminary skull radiography shows that it cannot succeed. When it fails, the next procedure should be the next safest, namely subtemporal rhizotomy. This policy would save an appreciable number of lives.

(3) *Drawbacks of treatment.*—All established forms of radical treatment have one outstanding drawback, namely paræsthesiæ, or dysæsthesiæ, felt in the affected area. Nearly every patient, if directly questioned, will say that he feels them, and many patients, even of an uncomplaining type, find them a real burden. They occur after rhizotomy of either sort, after alcohol injection, and also after medullary tractotomy according to most writers, including Grant (1948) and Falconer (1949). It may well be that they are connected with the transynaptic degeneration which Dr. Marion Smith has found in the nucleus of the descending trigeminal tract.

It is because of them that Dr. Palle Taarnhøj's operation[1] is so attractive, for, causing no sensory loss, it can cause no paræsthesiæ. He is right, however, to say that its efficacy is still unproved; by way of proof we need a series of at least 100 patients treated in this manner and all followed up for at least two years, at the end of which time the relapse rate will have to be as low as in a comparable series of subtemporal rhizotomies. One must remember that unsuccessful rhizotomies or injections are not infrequently followed by quite long remissions, presumably owing to vasodilatation and a temporary improvement in the blood supply of the trigeminal ganglion. At present it is not improbable that this new operation works in the same way, and no more permanently. One day surgeons may be able to construct new arterioles for the ischæmic trigeminal ganglion, just as they are now constructing new arteries for larger structures, and so provide a treatment without drawbacks. Let us hope, however, that Dr. Taarnhøj has given us such a treatment already.

(4) *Acceptability of cure to the patient.*—Some patients are not glad to be cured of any pain, however severe. The explanation in most cases is that their lives are devoid of activity and interest, they were so to speak married to their pain, and they find the sudden divorce distressing (Penman, 1954).

Much can be done to lessen most of these shortcomings. In letters to doctors, in articles in journals, and in the teaching of students and graduates, we can disseminate the idea that tic douloureux, though rare, is worth knowing about because it is unbearable, easily diagnosable, and curable. The diagnosis should be made on positive grounds, by means of a brief history. Treatment should not be attempted casually by the inexperienced; it should be radical; and the choice of method should be governed primarily by the death rate. All patients should be thoroughly warned of the drawbacks of treatment, and when a patient seems likely, on social and psychiatric grounds, to remain unhappy after cure, the help of his relatives should be enlisted beforehand. By these means we can make our treatment of this disabling disease actually satisfactory, instead of only potentially so.

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[1]Dr. Taarnhøj (Copenhagen) opened the discussion with an account of his operation for trigeminal neuralgia (*see J. Neurosurg.*, 1952, **9**, 288).

Dr. Marion C. Smith: Opportunities to examine post-mortem material from patients who suffered from tic douloureux are few, as the condition is not lethal.

I have had the opportunity of examining material from a few patients with this ailment, all of whom had received some form of treatment, and also material from patients with lesions of the V cranial nerve.

The general pattern of the trigeminal system.—In the trigeminal ganglion lie the cell bodies of the primary sensory neurones, in a dense semilunar mass; the axis cylinders of these neurones have a peripheral and a central division. The peripheral processes form the three main branches of the nerve: ophthalmic, maxillary and mandibular; the central processes form the sensory root, which enters the pons. The secondary neurones lie in two sensory nuclei, the "main sensory" which is associated with tactile sensibility and the descending or so-called "spinal" nucleus which is associated mainly, at least, with pain and temperature sensibility. A third nucleus, the mesencephalic, is thought to be composed of the primary neurones of proprioceptive fibres running with the motor root. The motor root runs with the mandibular division, and the nucleus lies medial to the main sensory nucleus.

In 3 of the cases I examined there was major trigeminal neuralgia or tic douloureux. In none of these cases have I found changes in the peripheral nerves, the semilunar ganglion, the sensory root, the sensory nuclei or any other part of the sensory pathway including the thalamus, which could be attributed to any other cause but the treatment given.

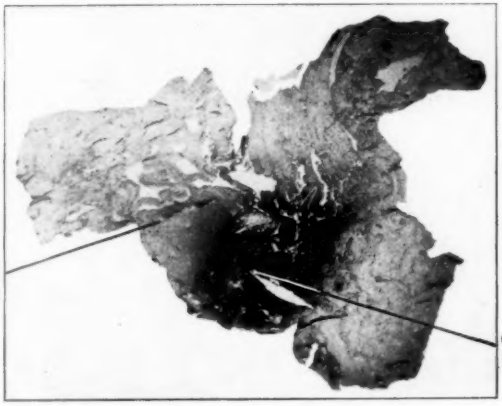

FIG. 1.—Trigeminal ganglion: cell mass injected with 3 c.c. absolute alcohol and hæmatoxylin after death. (Counterstained eosin).

Treatment of trigeminal neuralgia has been, most commonly, by interruption of the sensory pathway, either by alcohol injection or by section. When the peripheral divisions, only, of the nerve are destroyed, permanent analgesia cannot be expected, as only that part of the axon distal to the interruption degenerates, and regeneration of such peripheral nerves is usual. It is well recognized that complete section of the sensory root leads to permanent analgesia and anæsthesia. The permanence of damage by the action of alcohol on the nerves has been doubted. Dr. Penman and I published in 1950 a report on a case in which there was gross degeneration of the intracerebral part of the V nerve following injection of the ganglion. But it has been questioned whether this could not be a "freak" case, and not a true example of the results of injection.

Injection of the ganglion.—The unfortunate use of the word ganglion for both the cells and their central processes is misleading, and "injection of the ganglion" may mean injection into the cell mass, or into the plexus of sensory fibres. If one looks at a histological section through a ganglion in its widest plane, to obtain a view of the three divisions and of the root, the cells are seen to lie in a semilunar band. The central fibres are at first in a plexus, the pars triangularis, and then are more compact, the pars compacta. The band of cells varies in width in different sections and in different individuals. It is not a solid mass of neurones but is divided by continuations of the nerve fibres between groups of cells. In addition, many ganglia show little clumps of cells, separated away from the main band of cells, lying among the sensory root fibres. It is obviously very questionable whether an injection into this cell mass, itself, would permeate so as to reach all cells. To see if this were likely I dissected out a number of trigeminal ganglia from fresh cadavers, keeping them moist with normal solution and immediately on removal pinned them out on a piece of weighted cork, under saline. I then injected either absolute or 95% alcohol, containing hæmatoxylin, a histological dye with an affinity

for the nuclei of cells, into the cell mass of the ganglia through a Harris' needle. Amounts varying from 0·5 to 3 c.c. of alcohol, were used. The ganglion was then fixed in formalin, dehydrated, embedded in paraffin and sectioned. The sections were counterstained with eosin.

Such preparations are, of course, very crude, but they demonstrate the extent of action of the dye as shown in Fig. 1. The injected hæmatoxylin is limited to one area of the cell mass. In no ganglion was there more extensive colouring by the dye. It seems likely that the density of the cell mass and the fascicles of nerves running among the cells prevents spread of the alcohol. It would seem then likely that maximum destruction could be obtained if the injection was made into the nerve fibre region rather than into the cell mass itself. If made here, where the root becomes more compact, it would seem likely that the greatest number of fibres would be affected.

Fig. 2 shows a specimen from a patient of Dr. M. J. F. McArdle's, who died from a pulmonary embolus six days after injection. The injection was made into the mandibular division, 0·6 c.c. of 95% alcohol being injected, and the needle then advanced farther into the ganglion itself, and another 0·5 c.c. injected. The patient was analgesic in all three divisions until her death. The effect of alcohol in this case, histologically, was to fix the cells apparently, and alter them so that they resisted all the usual methods of histological staining. They appeared to be almost colourless in all preparations, and with the exception of a very few fibres, there was complete non-staining of axis cylinders in the mandibular division. There was an intense cell reaction in the neighbourhood of this pallid area. The injection would appear to have displaced the cells lying in opposition to the mandibular division. The cells opposite the maxillary division show some reaction. Elsewhere they are normal. There is gross degeneration in the sensory root.

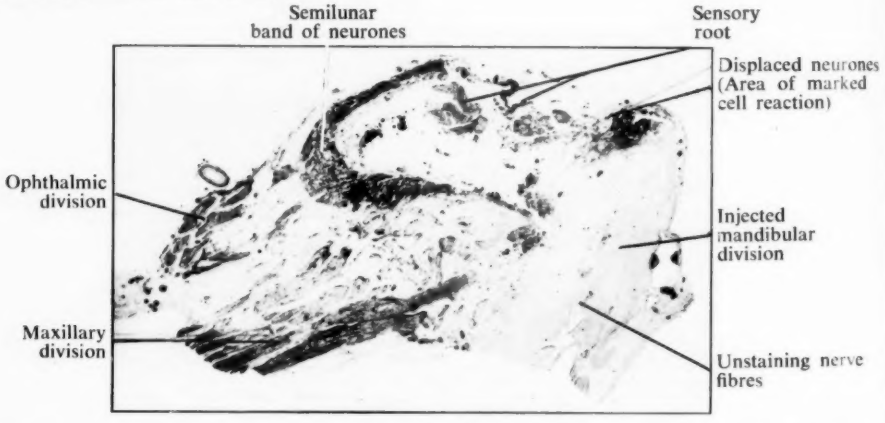

FIG. 2.—Trigeminal ganglion: injected with 95% alcohol 6 days before death. (Hæmatoxylin + eosin).

No case is known where functional regeneration of destroyed fibres has taken place in the central nervous system. We can therefore accept that the degeneration in these fibres is irreversible.

In this case degenerating fibres could not be traced beyond the main sensory nucleus. I do not suggest that further degeneration had not occurred, but only that it was not histologically demonstrable.

This case then shows that alcohol injection of the ganglion resulted in marked degeneration of the sensory root, which could be traced into the pons, six days after injection.

To demonstrate degeneration in the descending root of the V nerve, which is of importance in considering pain, it is necessary to refer to cases in which a longer interval occurred between operation and death. In the case of Dr. Penman's, to which I referred earlier, death occurred three months after injection of the ganglion.

In this case the descending fibres of the V nerve, on the injected side, are lost. This case then shows, as in the first, that with alcoholic destruction of sensory root fibres, the degeneration extends into the intracerebral pathway and may be therefore assumed to be permanent.

A further finding of interest in this case is the presence of degeneration in the ascending fibres of the secondary neurones. Degeneration of an axon cut off from its cell body usually does not lead to a demonstrable effect on the next neurone in the circuit. But in this case not only the primary axons but the secondary ones also show loss.

When Dr. Penman and I described this case we considered this degeneration to be an example of transynaptic degeneration. Although it seemed unlikely to us, it has subsequently been suggested that the fact that the lesion was caused by alcohol, and not by surgery, might have some bearing on

this degeneration. So I should like to describe now a case in which the lesion was caused by surgical section of the sensory root.

In this case of Dr. R. W. Nathan's, the sensory root was cut six months before death to relieve pain caused by a parotid tumour (Fig. 3). Here again there is a loss of fibres of both the descending root and the secondary ascending system.

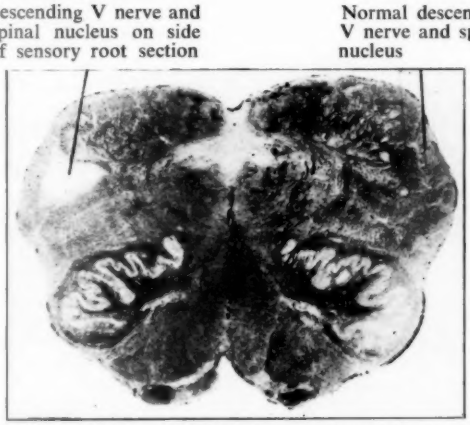

FIG. 3.—Medulla: on right side there is loss of both primary and secondary sensory fibres of V nerve after surgical section of sensory root. (Gros-Bielschowsky.)

In another case, in which the ganglion was destroyed by tumour, there was marked loss of both descending and ascending fibres.

It may be suggested, in view of the consistency of this finding of degeneration in the ascending fibres, that these medial lying fibres are *not* secondary fibres, but primary fibres also. But changes in cells of the ascending fibres can be seen. The neurones are mainly of small type, and to show degeneration in these small neurones is not easy. But scattered among them are larger cells, and some of these cells show chromatolytic changes. This is shown in Fig. 4, from the case in which the ganglion was destroyed by tumour.

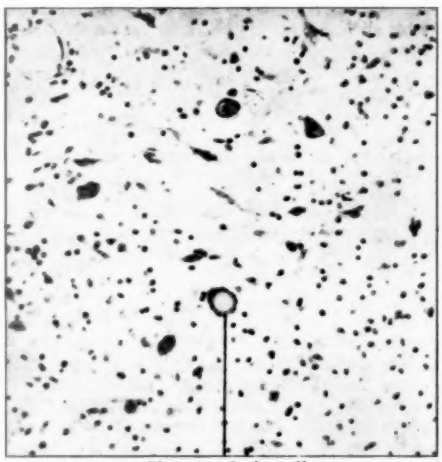

FIG. 4.—Spinal nucleus of V nerve: chromatolysis in secondary sensory neurone. Trigeminal ganglion on this side destroyed by tumour. (Nissl.)

It is necessary to exclude the possibility that these cells are primary neurones situated among the secondary neurones and exhibiting retrograde degeneration after a lesion of their axons in the

sensory root. This would seem to be highly improbable. Firstly, the existence of such neurones in this situation has never been described. Secondly, when an axon is damaged the distal part degenerates, the cell body may show changes, but the intervening length of axis cylinder remains unchanged indefinitely. If these were primary neurones we would then expect to see the persisting fibre in the descending sensory root. But there are no such intact fibres. To postulate the existence first of a new cell group, and then invoke that very rare occurrence of retrograde degeneration in fibres seems to be too improbable an explanation. And thirdly, in the first case with an interval of only six days between the injection and death, some of the cells of the V motor nucleus show retrograde chromatolysis, and in that case no chromatolysis was observed in the large cells of the descending root. But such chromatolysis might have been expected to be demonstrable in other primary neurones simultaneously with that in the motor nucleus.

The occurrence of actual loss of fibres supports the observation that these changes are transynaptic in secondary neurones, associated with destruction in the primary neurones. Why this occurs in the V nerve I do not know. I am constantly looking for it in the posterior column nuclei, and in cells of the posterior horn, in particular, after lesions of posterior roots, and have not seen it.

Sjöqvist showed that the number of fibres in the descending root remained pretty constant until the lower medulla, and he recommended tractotomy in the medulla at the level of the junction of the middle and lower thirds of the olive. He thought the arrangement of fibres in the descending root was mandibular-maxillary-ophthalmic in a dorso-ventral direction. This arrangement has been confirmed by most workers from clinical experience of medullary tractotomy, but occasionally a case is reported in which section of the ventral part of the tract only, confirmed at post-mortem, resulted in analgesia in the third division only. It would seem then, that the usual arrangement is mandibular-maxillary-ophthalmic in a dorso-ventral direction, but that variations of this may occur. Similarly, the caudal extent of the divisions in the root are considered to be: ophthalmic most caudal, maxillary slightly less caudal, and the mandibular ending a little below the junction of middle and lower thirds of olive. But in some patients at least, the mandibular division appears to end more caudally, and in others, more rostrally.

In one case (for which I am indebted to Dr. W. Blackwood) in whom section of the sensory root was followed by analgesia only, in the mandibular division, pallor of fibres could be seen in the lower medulla and could actually be traced as far as C.2. This is slender evidence, as it may be argued that this area of pallor did not represent degeneration in the mandibular division, but clinical observations of mandibular disturbance in a lower medullary or upper cervical cord lesion have frequently been made.

On the other hand, in a case of Dr. Smythe's, of posterior inferior cerebellar artery thrombosis, total destruction of the V nucleus was found here at the level of the rostral part of the olive—but there was complete analgesia of the first and second divisions only. It would seem, then, that some degree of variation in the caudal limit of the descending fibres also exists.

To sum up: If fibres of the sensory root are destroyed by alcohol, then degeneration of the intracerebral tract associated with the modality of pain is as permanent as the degeneration achieved by surgical section. Transynaptic degeneration occurs in at least some of the secondary sensory neurones. There is a pattern of distribution of the fibres of the three divisions, in the descending root of the V nerve, which appears to occur most commonly, but variants on this pattern are not infrequent.

I should like to thank all those who, by their generosity with their material, enabled me to make these observations.

REFERENCE

PENMAN, J., and SMITH, M. C. (1950) *J. Neurol. Psychiat.*, **13**, 36.

Mr. Geoffrey Knight: *Herpes Simplex and Trigeminal Neuralgia*

I have a personal experience of more than 200 cases of sensory root section, operated on without mortality, and including patients in whom this operation has been performed at the age of 82 and 84 years respectively.

Under modern conditions one can be confident of cutting the sensory root but that has not always been the case. In the days when anæsthesia and posture were less perfect and the difficulty of operation was greater, I, and all other surgeons, must admit that occasionally the sensory root was disturbed, but not divided. One learnt from that experience that any handling of the ganglion or sensory root without division was liable to produce a remission of pain extending over periods of six months to two years or longer. Bearing this fact in mind together with the known tendency of trigeminal neuralgia to undergo spontaneous remission, it would seem that no very definite significance can be attributed at present to the results of the so-called decompression operation on the sensory root. Not only has this operation failed to demonstrate any compressing lesion

but the average period of follow-up in the reported cases is so far only thirteen months, during which time a proportion of cases have already exhibited recurrent symptoms. The only thing which we know with certainty can happen, as the result of handling the trigeminal nerve, is the excitation of an outbreak of post-operative herpes simplex in the trigeminal territory.

Dr. Simon Behrman and myself have for long been interested in the possible connexion between herpes simplex infection and the clinical manifestations of trigeminal neuralgia. We believe that in discussing the pathology of trigeminal neuralgia, a condition in which, as Dr. Smith has shown, there is no demonstrable histological lesion, we must not lose sight of certain important features concerning the trigeminal nerve which are unique. The cutaneous area supplied by the trigeminus is the common site of herpes simplex, the trigeminus is the only nerve of which the handling is frequently followed by an eruption of herpes simplex, the trigeminus is the almost exclusive seat of paroxysmal neuralgia. There is a remarkable parallel between the clinical course of recurrent trigeminal neuralgia and recurrent herpes simplex infection (Table I).

TABLE I

Trigeminal neuralgia	Herpes simplex
Most common in women. 2–1 in 1,500 cases (Harris, 1937)	Recurrent outbreaks more common in women
Long remissions may occur	Long remissions may occur
Maxillary and mandibular distribution most frequently affected	Maxillary and mandibular distribution most frequently affected. (Also applies to post-operative herpes)

Dr. Behrman and myself believe that recurrent disturbances resulting from an infestation of the nerve by a herpes simplex infection can account for recurrent paroxysms of trigeminal pain. In support of this hypothesis we would quote three groups of cases: Those in which pain in a particular area of the trigeminus may precede herpes simplex outbreaks affecting the same area of the face; those cases in which attacks of trigeminal pain are accompanied by herpetic outbreaks, and lastly, those cases in which the pain may develop or even change sides following an outbreak of herpes simplex. Three cases of the first group, occurring in the practice of Dr. Behrman, in which typical recurrent trigeminal neuralgia regularly preceded the appearance of herpes simplex outbreaks in the same area as the pain, are summarized in Table II.

TABLE II.—TYPICAL RECURRENT TRIGEMINAL NEURALGIA FOLLOWED BY APPEARANCE OF HERPES SIMPLEX OUTBREAKS

Name	Age	Duration of illness	Duration of paroxysms	Period by which attacks precede appearance of any eruption	Site of pain	Site of eruption
Mrs. F.	32	20 years. Attacks every 3–4 weeks	Typical momentary paroxysms	Several days	Maxillary division.	Maxillary division upper lip and cheek
Nurse H.	46	4 years. 4 attacks in all	Typical momentary paroxysms	1 week	All 3 divisions	All 3 divisions
Miss P.	47	8 years	Typical momentary paroxysms	4–5 days	Second division right	Second division. Also eruption in second division without associated pain

The further history of the last of these cases is particularly interesting. In 1945 a right-sided sensory root section was performed for the relief of her pain, and was followed by outbreaks of post-operative herpes on the upper lip and recurrent attacks of simple herpes in the anæsthetic skin area. In 1947 she developed post-auricular and occipital neuralgia associated with herpes simplex outbreaks. In 1948 she developed a massive eruption of herpes simplex in the right second division area which led to ulceration of the ala of the nose. It will be noted that all her trouble, so far, has been situated on the right side but in 1951 she developed a pyrexial illness. Her temperature rose to 101° F. and was followed on the next day by an outbreak of herpes simplex on both sides of the face including the left upper lip and left side of the mouth, and on the following day she developed *left*-sided trigeminal neuralgia involving the maxillary division followed by typical recurrent attacks in that division, later extending to involve the third division as well, in the course of the succeeding three years. This case appears to us to be highly significant as indicating that typical trigeminal neuralgia may develop for the first time following a herpetic outbreak, and this fact, taken in association with the other evidence that paroxysms of trigeminal pain may regularly precede the

development of herpetic outbreaks occurring in the same area as the pain, may indicate that the affected branches of the trigeminus are the seat of a herpetic infection.

It is known that the virus of herpes simplex possesses neurotrophic propensities. In 1923 J. S. Friedenwald, an American ophthalmologist, showed that the inoculation of the virus of herpes simplex into the conjunctiva of rabbits produced herpetic keratitis and encephalitis. He demonstrated inclusion bodies and active virus in the gasserian ganglion and suspected that the virus entered the central nervous system through the sensory root. In 1925 Goodpasture and Teague showed that in contact infection in rabbits, the virus entered the brain through the sensory divisions of the nerve supplying the mucous membranes of the mouth and throat and demonstrated inclusion bodies in the nuclei of the V and IX cranial nerves; a curious point this, bearing in mind the similarity of trigeminal and glossopharyngeal neuralgia. It is not impossible that virus infection of a nerve should produce long-lasting pain. Following virus infestation with herpes zoster a neuralgia of a different type persisting throughout life may develop in a small proportion of infected individuals, and there is, after all, a clinical parallel between infection with herpes zoster and trigeminal neuralgia. If the trigeminal territory is the seat of herpes zoster infection there is a selective involvement of certain areas and a sparing of others. Trigeminal neuralgia and post-herpetic zoster neuralgia are conditions usually met with in elderly individuals; senescence is a factor in both forms of neuralgia.

The observations of Carton and Kilbourne (1952) are often quoted as disproving any possibility of herpes simplex infection being the cause of trigeminal neuralgia, since these observers were unable to isolate the virus from the ganglion or sensory root; but that does not exclude the presence of a peripheral infection in relation to terminal endings. What is the significance of trigger areas, the pain spots which are seen so characteristically in this condition and in no other? That the virus of herpes simplex is present in the majority of cases of trigeminal neuralgia is evidenced by the fact that complement-fixation tests are positive in 100% of cases tested, and I think it is correct to state that the President of the Section has observed that recurrent herpes can occur in the presence of a high concentration of antibodies. There is, likewise, the high incidence of post-operative herpes. Certain American observers claim that vesicles, detected with the aid of a lens, may be seen in 90% of patients. We have estimated that vesicles visible to the naked eye are present in 60% of the 175 cases operated on at the South East Metropolitan Regional Neurosurgical Centre.

There is sometimes a very close relationship between the distribution of the post-operative herpes and the distribution of the pre-operative pain, and I would like to quote one final case. A Mrs. E. S. had for three years suffered from severe recurrent neuralgia involving the second division of the nerve. A complete sensory root section was performed producing complete anæsthesia in all 3 divisions in April 1947. Two days later she developed a massive outbreak involving the whole territory of the second division associated later with crusting in the nose and ulceration of the ala, which was so severe that in April 1948 I referred her for plastic repair to Mr. F. T. Moore who produced a most satisfactory cosmetic result by grafting in a portion of the cartilage of her ear. It appeared to me to be something more than a coincidence that so severe an outbreak should be confined exclusively to the territory of the second division, which had been the principal site of her pain, in a patient in whom the entire sensory root had been divided. Bearing these facts in mind, together with the negative character of any alternative evidence, I would suggest that the possibility of virus infection being the cause of trigeminal neuralgia is well worthy of further consideration.

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BOOK REVIEWS

Recent Developments in Psychosomatic Medicine. Edited by E. D. Wittkower, M.D., and R. A. Cleghorn, M.D. (Pp. xvi + 495. 50s.) London: Pitman. 1954.

The Editors of this book feel that psychiatric interest should not be confined to those bodily diseases where psychological factors are known to be ætiologically important. Thus, the problems involved in the nurture of a diabetic child are examined; and so are the connexions between social attitudes to sex and venereal disease. The questions arising from disablement are also examined in some detail. This is a perfectly legitimate view to take and the Editors have stated it clearly, with the melting addition that psychosomatic medicine must inevitably be dedicated to its own dissolution. Inevitably the book contains much that is speculative and controversial but this, too, is stated quite fairly by the Editors, and lends the book special interest and value.

The general reader must, of course, be prepared for some shocks. He will read that in respiratory disturbances "there are three features which are outstanding: (1) a longing, (2) directed originally toward the mother, (3) taking the form of a respiratory intra-uterine relationship". Nevertheless it is a notable feature of this book that these views do not obtrude themselves unduly. In the chapter on peptic ulcer, for example, the writer's general orientation is Freudian but this does not prevent the history of psychiatric thought about peptic ulcer being laid fairly and adequately before the reader. The chapter ends as all the others do, with a well-selected and comprehensive bibliography.

The first three chapters give an excellent survey of the basic concepts and history of psychosomatic medicine though they are perhaps a shade on the polysyllabic side for easy reading. Individual diseases are dealt with fairly comprehensively though there are some omissions since the book deals with recent advances. Anorexia nervosa and mucous colitis in adults are omitted. Some of the surveys are of a comprehensive kind and the chapters on Endocrines by Dr. R. A. Cleghorn, the Limbic System by Dr. P. D. MacLean, and that on the Psychiatry of Obstetrics and Gynæcology by Dr. Desmond O'Neill are of outstanding excellence.

The diagrams are plentiful and clear; and the paper is of very good quality. There is an index of authors, and the subject index appears comprehensive. Even at fifty shillings it is very good value.

Mechanisms of Urologic Disease. By D. M. Davis, M.D. (Pp. 156. 22s. 6d.) Philadelphia and London: W. B. Saunders and Co. 1953.

This book, as stated by its author in the preface, was begun as a series of introductory lectures to third-year students. It has no pretensions to being a textbook on urology but does provide an introduction to this subject for those on the threshold of a medical career. Instead of the various diseases being described according to the organs involved, as is the usual custom, they are discussed from the standpoint of pathology; thus infection is considered as a whole, and not in relation to a particular part of the urinary tract. For the beginner this method of presentation has much to commend it.

The author, wisely, gives no detailed descriptions of operations. For the treatment of simple enlargement of the prostate the anatomical routes for surgical approach to the gland are briefly recorded. No dogmatic statements are made in favour of any particular operation. There are a few charts but no illustrations. There is a chapter on catheterization which gives sound advice on its uses and abuses. The final chapter has the title of "Outline for history taking and physical examination". It should be helpful to those responsible for note taking. At the end there is a list of books recommended for reference. The student, at the outset of his clinical studies, will find this little book of much use to him.

Medical and Scientific Investigations in the Christie Case. By Francis E. Camps, M.D. (Pp. 240; 6 coloured plates and 46 figures. 30s.) London: Medical Publications Limited.

How many have succeeded in disposing of the body and thus have escaped trial will never be known. Many murderers have tried and have paid the penalty of failure: each of them has dangled later at the end of a rope. The problem is as old as murder itself.

In the years before March 1953 when he was arrested John Reginald Halliday Christie murdered six women including his wife at 10, Rillington Place, a drab cul-de-sac west of Ladbroke Grove, London, W.11. Four of the bodies he hid in the house; two he buried in the garden.

If a tenant sharing the kitchen on the ground floor had not wanted to fit a shelf for a wireless set Christie might have escaped for longer than he did. But the tenant came across a hollow space covered with wall paper and on stripping it off found a cupboard door behind which there was sitting the naked body of a dead woman. The police later found two more bodies of women behind the first body and later still they found the body of Christie's wife under the floor boards and two skeletons in the garden.

Thus was started one of the most remarkable cases in criminal records, for multiple murders are rare here.

Christie was responsible for bringing into action all the resources of the forensic laboratory, and this book by Dr. Francis E. Camps, Lecturer in Forensic Medicine at the London Hospital Medical College, who himself took a considerable part in the medical examinations, is an account of the work which was done by him and by the distinguished team which was mobilized to discover what was to be learnt from an examination of the remains.

Flesh, bones, teeth, jaws, and hair all came in for expert examination to determine sex, age, stature, cause, and approximate date of death.

From the miserable hovel in Rillington Place Christie sent out a challenge to forensic medicine over which the specialists triumphed.

To determine the age and height and to state the sex in life of each of two skeletons whose bones and teeth have been scattered and mixed beneath a garden; to arrive at conclusions from four clumps of pubic hair found in a tobacco tin; and to draw the proper inferences from signs on exhumation are some of the tasks on which this team was engaged. Success was achieved. The outstanding case of Christie is one of the high-water marks of forensic pathology.

Dr. Camps has written an excellent book which should be in the hands of every student and practitioner of this attractive and important branch of medicine which makes so great a contribution to the investigation of crime.

Not only was there co-operation in the course of the case but there has also been collaboration in the production of the book. One has only to mention such names as Mr. L. C. Nickolls, Director of the Metropolitan Police Laboratory, New Scotland Yard; Dr. Richard J. Harrison, Professor of Anatomy, London Hospital Medical College; and Professor A. E. W. Miles, of the London Hospital Dental School, to indicate the value of this work.

Atlas of Descriptive Human Anatomy. Vol. III. *Blood Vessels, Nervous System, Sense Organs and Integument and Lymphatics.* By Dr. J. Sobotta. Edited and translated by Professor Eduard Uhlenhuth, Ph.D. 5th English edition. (Pp. xix + 390; 306 illustrations. £6 5s.) London: Lange, Maxwell and Springer Ltd. 1954.

Sobotta's Anatomy has been better known in the United States of America and on the continent of Europe than in Britain, where Spalteholz's three volume work has been popular. This is the first English edition, and the publishers hope to issue English translations of Volumes I and II shortly.

It is impossible to speak too highly of this Atlas. The illustrations, the great majority of which are in colour, are of actual dissections, and they show not alone the organ or system they are intended to illustrate, but the bones, muscles, nerves and vessels with which it is in relation. In Volume III the blood vessels, the peripheral nerves, the brain, the sense organs and the lymphatics are dealt with in turn. As an accompaniment to a dissecting manual, as a means of revising a part when dissected, as an aid in preparing for a test such as the Primary Examination of the Fellowship of the Royal College of Surgeons this book will be found invaluable. Even the mature surgeon who has one or several Fellowships will find it useful in refreshing his memory before tackling an unusual or difficult operation.

The Hepatic Circulation and Portal Hypertension. By Charles G. Child, III, M.D., Professor of Surgery. (Pp. 444; illustrated. 60s.) Philadelphia and London: W. B. Saunders and Co. 1954.

The fact that the Section of Surgery in the Royal Society of Medicine has devoted an evening to a symposium on Portal Hypertension within the past year is an indication of the interest that this subject is arousing in Medicine today. A few years ago, alcoholic cirrhosis and an ill-defined syndrome known as Banti's disease covered all that was known clinically about the disturbances of the portal circulation, and splenectomy and the Talma-Morison operation comprised the whole of surgical treatment. Since that time the knowledge that cirrhosis may follow many infections and the operation of many toxins other than alcohol, the introduction of new diagnostic methods such as improved radiography, portal venography and portal manometry, the greater safety of exploration in poor-risk patients brought about by better anæsthesia and the use of antibiotics, and the fresh methods

of treatment introduced by the perfection of vascular suture, have led to intensified study, and have brought into medical terminology the general term Portal Hypertension to include a group of diseases of differing ætiology having in common the fact that they are characterized by a rise in the portal blood pressure, and that they may be accompanied by ascites and dangerous hæmorrhage from œsophageal varices.

Dr. Charles Child's book therefore appears at an opportune moment. In his preface he says: "The subject of the liver and its related vascular structures substitutes a large research and clinical field sorely taxing the abilities of any one essayist." Dr. Child's ability and his industry have proved equal to the task, and he has given us a book that will be valuable to the clinician and the scientist.

The physician or surgeon who is concerned with diseases of the liver, who is contemplating any research work, or who wishes to base his treatment on sound foundations will find this book indispensable, for the historical review, and the analysis of research work it presents, are masterly. There is also much sound practical advice for the clinician. Thus:

"Although too early to generalize on the ultimate place of portal decompression in the treatment of portal hypertension, it seems reasonable to say that bleeding can be effectively controlled when it is possible to construct an adequate anastomosis. In unselected cases, sodium and water retention appears to be aggravated rather than improved as a result of portal decompression. It also appears probable that relief of portal hypertension does little if anything to alter the relentlessly progressive course of the liver failure which constitutes the natural history of cirrhosis of the liver" (p. 258).

"*Cirrhosis: Without Hæmorrhage or Varices.* Patients in whom a diagnosis of varices cannot be made with relative ease and who have never bled should, in the light of present knowledge, not be operated upon. Portal decompression does not, as far as is known, improve hepatic function nor does it increase the reserve of this organ. There seems, therefore, little reason to decompress the portal bed in patients with uncomplicated cirrhosis" (p. 265).

"*Cirrhosis with Uncontrolled Ascites.* In line with Eck's original suggestion, many have been persuaded that a successful portacaval shunt would prove useful in controlling ascites. As soon as the technique for performing such a shunt successfully was developed, many patients with ascites were operated upon with this as the primary indication. The results have been uniformly disappointing. Not only was the ascites unaffected, but the post-operative mortality proved prohibitively high." (p. 266).

This book can be recommended whole-heartedly. It is well reproduced and well illustrated, and no one can read it without gaining a fresh insight into the subject of Portal Hypertension.

The Anatomy of the Bronchial Tree. By R. C. Brock, M.S., F.R.C.S. 2nd edition. (Pp. vii + 243; 157 illustrations. 45s.) London: Oxford University Press. 1954.

The appearance of a second edition of Sir Russell Brock's classical monograph is indeed welcome. When first he published his researches into the anatomy of the bronchi, regarded from the standpoint of practical surgery, he emphasized the neglect of accurate study in this direction, a neglect which he himself has in the last few years done so much to remedy by the patient attention to detail and the tenacity of purpose which characterize all his work. To the thoracic surgeon this volume is indispensable; it should moreover find a prominent place in the library of every physician who professes a special knowledge of chest disease.

In this edition the essentials of the applied anatomy of the bronchi remain much as they were in his original publications. The chief alterations in the text are those arising from the adoption of the standard nomenclature drawn up by the International Committee in 1949 and published in *Thorax* (1950, **5**, 222). The author has always been a strong advocate of such standardization, and the care which he has taken in the revision of this work is a testimony to his convictions in this matter.

The rearrangement of many figures in relation to the text will contribute not a little to the reader's comfort. It is difficult always to make a fair comparison of illustrations, but we have the impression that in this edition many of the pictures appear clearer and better reproduced than the corresponding ones in the first edition. We note this especially in the reproduction of injected and dissected specimens and in several of the diagrammatic drawings. The appendix on the mode of preparation of specimens is of much interest, though it may, perhaps, appear a little superfluous to some readers, who will value the book mainly as a guide to the practising thoracic surgeon. The addition of an index in this edition is a useful improvement on its predecessor.

Surgical Forum. Clinical Congress of the American College of Surgeons, 1953. Vol. IV. (Pp. 752. 50s.) Philadelphia and London: W. B. Saunders and Co. 1954.

Surgical Forum reprints in book form the papers dealing with surgical research presented at the Clinical Congress of the American College of Surgeons. This volume contains those read at the meeting held in Chicago in October 1953. It includes about one hundred and forty papers grouped under the headings of Heart and Great Vessels, Blood Vessels and Circulation, Lungs, Œsophagus, Stomach and Intestine, Liver and Pancreas, Burns and Renal Function, Shock Nutrition and Electrolytes, Wounds, Cancer and Plasma Expanders.

To call these papers the front line of surgical advance is a little too modest. They are the preliminary reports of young Commandos venturing into no-man's land or far away into enemy territory, and many of them may prove to be wrong when the main body reaches where they are now. But they are stimulating.

In the section devoted to the Heart, there is much about hypothermia and the closing of septal defects in vascular surgery, much about peripheral vascular disease and the use of grafts. In the abdominal section there are many papers on Peptic Ulceration and Portal Hypertension; in the section on Shock, which is the largest, any number of studies on the chemistry and dynamics of the circulation.

This is a research publication, pure and simple, but as such it is an important yearly addition to any surgical library.

The Parietal Lobes. By Macdonald Critchley, M.D., F.R.C.P. (Pp. 480. 70s.) London: Edward Arnold and Co. 1953.

The literature upon the complex symptomatology of lesions involving the parietal lobe has grown apace of late years, as may be seen from the bibliography of over 1,000 papers appended to this monograph.

The author's own contributions to the subject are considerable, and thus he has been able to provide a monograph not only exhaustive in its scope, but also critical. In doing so he has placed his neurological colleagues in his debt for a work that will be indispensable to them as a work of reference, and as a stimulus to thinking upon this fascinating subject which bestrides the frontier between physiology and psychology, and is not without its philosophical implications for those able and willing to consider them.

If the author has not been able to make his subject appear simple, it is because the complexity of the disorders observed has taxed the ingenuity of the clinical observer and the classifier, and because, also, the passion for dipping into the lexicon for ever more neologisms has been indulged in by writers on the parietal lobe syndromes to a degree never exceeded in the literature of neurology.

There are few symptoms that have not more than one name, and few names that have not more than one meaning. Even so important an operative term as "body image" does not mean the same thing or notion to every one that uses it.

Nevertheless by his lucidity Dr. Critchley has placed before his readers intelligible descriptions of all the main disorders and of their characteristic combinations in lesions of one or other hemisphere.

Here is the raw material from which an ordered physiology of the sensory functions of the cerebral hemispheres may one day be built: when terminology becomes precise and has been ruthlessly pruned, and when students learn to distinguish between the symptoms of lesions and normal functions: between data of observation and theoretical conclusions which are not observed but deduced.

The study is one which only the clinician with the human subject can hope to develop, and once the necessary conditions of method—that is, intellectual method rather than technical—have been established, the chapter on the parietal lobes may form one of clinical neurology's most brilliant contributions to neurophysiology.

Section of Epidemiology and Preventive Medicine

President—A. BRADFORD HILL, C.B.E., F.R.S.

[*May* 21, 1954]

Poliomyelitis in England and Wales Between the Wars

PRESIDENT'S ADDRESS

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THE starting point of the study here reported was a press reference in the early summer of 1953 to poliomyelitis being epidemic in the County of Essex. I could recall at least three previous epidemics in that same county. But, remembering that Essex is a large county, was there anything odd about that? Was it merely due to chance or were there localities in this country which poliomyelitis specially tended to visit or in which it particularly cared to linger? In an attempt to answer those questions I set about extracting the relevant information, based upon the notifications published in the weekly and annual reports of the Registrar General of England and Wales.

THE NOTIFICATIONS OF POLIOMYELITIS

Poliomyelitis first became notifiable in this country in 1912 but, avoiding the years of the First World War as possibly atypical, I took the year 1919 as my starting point. Whilst I was delving into the records of these early years Benjamin and Logan (1953) published an article on the "Geographical and Social Variations in the incidence of Notified Poliomyelitis". Their field of study was directed, however, to the large-scale epidemics of recent years, 1947–50. This enabled me to bring my own observations to an end in the year 1946 and yet to be in a position to compare past with present. What I have called "between the Wars", is, therefore, roughly the period between their two conclusions, namely 1919 to 1946.

There will, of course, be much error in the original uncorrected notifications. The hospital survey of 1947 made by Bradley and Gale (1949) showed that among 6,762 patients admitted to hospital with a diagnosis of poliomyelitis, or polio-encephalitis, the diagnosis was subsequently confirmed in only about 70%. On the other hand, in earlier years the error might lie rather in omission than addition—that, in particular, the non-paralytic case would go unreported. For example Bruce Low in his report to the Local Government Board in 1915/16 wrote that "there is evidence that in some towns poliomyelitis is endemic though attracting little attention. For example, in the borough of Sunderland, which had, in 1911, a population of 165,295, paralysed children are brought year after year to the Sick Children's Hospital where the true nature of the ailment is recognized. In 1912 the hospital books show that 8 such cases were treated; 10 in 1913, 9 in 1914, 12 in 1915. On the other hand, the Medical Officer of Health for the borough only received six notifications of poliomyelitis between September 1912 and March 1916" (Low,1916). His reference is to the early years of notification (and of war) which I deliberately excluded from my account. But, clearly, such errors will have continued throughout all years, on some unknown scale and with, quite possibly, changes taking place with the passage of time. They must inevitably blur the picture I put forward, they may even so distort it as to make it worthless. That we must consider.

THE CALCULATION OF EXPECTED CASES

In their study of the large-scale epidemics of 1947–50 Benjamin and Logan compared the recorded notifications in each administrative county and county borough with those that would have occurred in each such area or town if it had suffered the average attack rate that had prevailed in all England and Wales. I have followed the same procedure for the earlier years. In each year 1919–1946 I first calculated the attack rate in all England and Wales (notifications/total population), and then in each year separately I applied the attack rate to the mid-year population of each administrative county and each county borough. The observed and "expected" cases in each area I then summed

into three periods—1919–28, 1929–38, and 1939–46. Taking the ratio of the observed to the expected cases I can compare these results with those found by Benjamin and Logan. For this purpose I grouped the counties and county boroughs into four groups on the basis of their observed/expected ratios in 1947–50 (regardless of the standard errors and statistical significance of the ratios). The four groups I took are:

(1) Areas with observed cases less than 66% of those expected in 1947–50
(2) ,, ,, ,, ,, 66–99% ,, ,, ,, ,, ,,
(3) ,, ,, ,, ,, 100–133% ,, ,, ,, ,, ,,
and (4) ,, ,, ,, ,, 134% or more ,, ,, ,, ,, ,,

The observed/expected ratios for these same groups in earlier years are set out in Tables I and II.

TABLE I.—THE RATIO OF OBSERVED (O) TO EXPECTED (E) CASES IN GROUPS OF ADMINISTRATIVE COUNTIES

Groups of Administrative Counties		Period of years 1947–50	1939–46	1929–38	1919–28	1919–46
Group I. 8 A.C.s with observed cases less than 66% of the expected in 1947–50	O	520	175	202	203	580
	E	990	224	246	230	701
	%	*53*	*78*	*82*	*88*	*83*
Group II. 24 A.C.s with observed cases 66–99% of the expected in 1947–50	O	7,340	1,714	1,958	1,476	5,148
	E	8,330	1,776	1,912	1,620	5,307
	%	*88*	*97*	*102*	*91*	*97*
Group III. 21 A.C.s with observed cases 100–133% of the expected in 1947–50	O	7,445	1,843	1,665	1,351	4,859
	E	6,710	1,454	1,523	1,285	4,261
	%	*111*	*127*	*109*	*105*	*114*
Group IV. 8 A.C.s with observed cases 134% or more of the expected in 1947–50	O	906	168	181	152	501
	E	508	112	121	110	343
	%	*178*	*151*	*149*	*138*	*146*
Group V. London A.C.	O	2,743	339	745	745	1,829
	E	2,147	417	700	701	1,818
	%	*128*	*81*	*106*	*106*	*101*

TABLE II.—THE RATIO OF OBSERVED (O) TO EXPECTED (E) CASES IN GROUPS OF COUNTY BOROUGHS

Groups of County Boroughs		Period of years 1947–50	1939–46	1929–38	1919–28	1919–46
Group I. 32 C.B.s with observed cases less than 66% of the expected in 1947–50	O	1,120	314	500	454	1,268
	E	2,288	489	617	573	1,678
	%	*49*	*64*	*81*	*79*	*76*
Group II. 28 C.B.s with observed cases 66–99% of the expected in 1947–50	O	2,373	448	616	648	1,712
	E	2,767	581	700	600	1,879
	%	*86*	*77*	*88*	*108**	*91*
Group III. 15 C.B.s with observed cases 100–133% of the expected in 1947–50	O	2,313	520	561	532	1,613
	E	2,083	490	585	527	1,602
	%	*111*	*106*	*96*	*101*	*101*
Group IV. 8 C.B.s with observed cases 134% or more of the expected in 1947–50	O	2,549	301	348	440	1,089
	E	1,486	317	366	323	1,006
	%	*172*	*95*	*95*	*136*	*108*

*If the exceptional epidemic in Kingston-upon-Hull be excluded this percentage falls to 93.

THE CONTRAST OF 1947–50 WITH EARLIER PERIODS

It is clear that with the administrative counties (Table I) the four groups have tended to occupy the same position in each of the four periods of time. Those with relatively low attack rates in the wide-scale epidemics of 1947–50 experienced also, on the average, a relatively low attack rate during the years of 1919–46 when the incidence of the disease in this country was small. To counties with relatively high rates in 1947–50, high rates were no new phenomenon. The same type of picture is revealed by the county boroughs (Table II) but it is certainly less distinct. In terms of correlation coefficients these associations are shown in Table III.

TABLE III.—THE DEGREE OF CORRELATION BETWEEN THE RATIOS OF OBSERVED TO EXPECTED CASES IN (*a*) 1947–50, (*b*) EACH EARLIER SPECIFIED PERIOD

	1919–28	1929–38	1939–46
Administrative Counties (62)	0·26	0·45	0·33
County Boroughs (83)	0·10	0·19	0·23

THE GEOGRAPHICAL VARIATIONS IN 1919–46

For the years 1919–46 as a whole the geographical vagaries underlying these associations are shown in Map I (in which the county boroughs have been included in the administrative counties—they

MAP I.—COUNTIES OF ENGLAND AND WALES. OBSERVED/EXPECTED CASES IN 1919–46
A.C.s Together with Associated C.B.s

usually, but not always, behave in the same fashion). The most striking characteristics of the distribution are the significantly low ratios of the northern and most of the Welsh counties, and the significantly high ratios of, perhaps, three distinct groups of counties, (*a*) the East Riding of Yorkshire, Lincolnshire (Parts of Lindsey and Kesteven), Leicestershire and Rutland, (*b*) Herefordshire and Shropshire on the Welsh borders and extending into Radnor and, probably, Montgomery, and (*c*) a long southern belt of counties stretching across the country from Devon, and probably Cornwall, to Essex and Kent. Correlating these ratios for 1919–46 with the corresponding ratios for 1947–50 gives a coefficient of 0·43. In other words there was quite an appreciable degree of similarity in the geographical scatter of poliomyelitis in its days of low incidence in 1919–46 and in its widespread epidemicity in 1947–50.

Can this similarity, these geographical differences, be explained wholly in terms of inaccurate diagnosis or of notification? I would have thought not. For instance, most of the Welsh counties have low rates; yet where they touch the borders of Hereford and Salop cases do not go undetected; the counties of Radnor and Montgomery have distinctly unfavourable experiences. The year-after-year deficiency in the northern and north-western counties does not prevent repeated, though small, epidemic outbreaks being detected and reported in Westmorland. The little group of counties (Parts of Holland (Lincolnshire), Cambridge, Ely, Peterborough, Northamptonshire, Bedfordshire and Huntingdon) is hemmed in by areas of relatively high incidence to north and south. Yet their observed cases in 1919–46 (366 in total) were 13% below expectation.

Further contrasts are given numerically in Table IV. That the observations and habits of so many

doctors can vary so considerably over so long a span of years in these closely contiguous areas would not seem to be very likely. To seek some other explanation would, therefore, seem justifiable and, possibly, profitable.

TABLE IV.—SOME SELECTED EXAMPLES OF OBSERVED AND EXPECTED CASES

Counties with associated County Boroughs	1919–28			1929–38			1939–46		
	Obs.	Exp.	Ratio	Obs.	Exp.	Ratio	Obs.	Exp.	Ratio
Westmorland	29	9	*322*	17	10	*170*	36	10	*360*
Cheshire and Lancashire	633	937	*68*	741	1,024	*72*	665	876	*76*
Lincolnshire, Kesteven and Lindsey	102	79	*129*	217	89	*244*	143	79	*181*
Nottinghamshire	93	102	*91*	78	121	*64*	91	112	*81*
Herefordshire and Salop	74	55	*135*	71	58	*122*	85	57	*149*
Staffordshire	204	216	*94*	152	242	*63*	218	217	*100*
Oxfordshire	58	29	*200*	101	36	*281*	76	38	*200*
Bedfordshire	24	32	*75*	25	39	*63*	46	43	*107*

THE GEOGRAPHICAL VARIATIONS IN DETAIL

(a) Towns.—In promoting the search a more detailed picture of the main areas of epidemicity must first be constructed. In so doing I studied the year-by-year variations in recorded incidence in each individual city and county both in relation to their annual movements, up or down, between 1919 and 1946, and also with regard to the number of cases actually observed in any given year as compared with those that might have been expected at the average rate of that year (i.e. the rate for all England and Wales). With these criteria I endeavoured to pick out all the most striking epidemic events of these twenty-eight years. In the process many small foci—a dozen cases in a town when two or three would have been expected—were, of course, omitted. Even those selected will very often have had quite low attack rates in relation to the populations at risk but they *were* distinct epidemics, i.e. in terms of those pre-1947 days of, in this country, low poliomyelitis incidence.

The relevant figures for the county boroughs are given in Table V. It may be noted that of the total

TABLE V.—COUNTY BOROUGHS EXPERIENCING EPIDEMICS IN GIVEN YEARS
(in Brackets Observed and Expected Cases)

Bristol	1919 (17, 6); 1921/22 (40, 9); 1929 (18, 5); 1938 (24, 15).
Oxford	1919 (18, 1); 1932/34 (15, 3); 1938 (34, 3); 1941 (29, 3).
Sheffield	1922 (19, 5); 1924 (53, 10); 1931 (45, 4); 1932 (24, 8).
Plymouth	1919 (18, 3); 1921 (18, 3); 1928 (13, 2).
Kingston-upon-Hull	1927 (109, 6); 1933 (36, 6); 1938 (25, 4).
Cardiff	1923 (46, 3); 1924 (22, 4); 1940 (43, 6).
Portsmouth	1934 (27, 4); 1938 (19, 9); 1944 (10, 2).
Manchester	1936 (30, 10); 1939 (31, 12); 1941 (31, 15).
Birmingham	1923/24 (74, 33); 1935 (26, 16); 1940 (55, 28).
Leicester	1926 (80, 7); 1938 (26, 9).
Grimsby	1930 (36, 1); 1938 (17, 3).
Wolverhampton	1940 (25, 4); 1945 (16, 3).
Liverpool	1923 (37, 13).
Merthyr Tydfil	1923 (21, 1).
Nottingham	1926 (31, 8).
Leeds	1940 (26, 13).
West Ham	1937 (18, 5).
Reading	1938 (17, 4).
Swansea	1938 (40, 6).
Lincoln	1941 (17, 2).

83 boroughs only 20 appear here as having shown a substantial epidemic spread during the twenty-eight years and only 12 have had more than one distinct outbreak. On the other hand there are 9 large towns in which poliomyelitis was epidemic three or four times in this quarter of a century, viz. Bristol, Oxford, Sheffield, Plymouth, Kingston-upon-Hull, Cardiff, Portsmouth, Manchester and Birmingham. Is this mere chance or has any special environmental characteristic tended to bring these cities to the forefront? It seems idle to seek the answer in general socio-economic conditions as measured by the proportion of unskilled workers, infant mortality, housing density and so on. Various workers have already failed to discover any such associations (Benjamin and Logan, 1953; Daley and Benjamin, 1948; Hill and Martin, 1949). There is, however, one possibly relevant feature, namely the large number of ports which appear in the list. Of the total 20 towns, half are ports (including West Ham under the port of London) while of the leading 9 towns with several epidemic experiences 6 are ports (the exceptions are Oxford, Sheffield and Birmingham). It would seem possible, therefore, that in these years of low prevalence in England and Wales quite frequent introductions of the disease were being made from abroad but that these introductions did not succeed in spreading

seriously or very far afield. To take two examples: In 1927 there was a particularly severe epidemic in Kingston-upon-Hull—109 cases in a population of 297,000 or a rate of 37 per 100,000 persons. There was some spread to immediately adjacent areas for a rise is shown in the East and West Ridings, in Leeds C.B. and in the Parts of Lindsey in Lincolnshire. The rest of the country appears quite unaffected. Three years later, in 1930, there was an outbreak of the same relative magnitude in Grimsby, 36 cases in a population of 92,000 or a rate of 39 per 100,000. The Parts of Lindsey, Lincolnshire, were also heavily affected but almost entirely on the eastern side of the County and particularly in Cleethorpes U.D. and Grimsby R.D. There was a slight spread in Northamptonshire. The rest of the country appears free.

(*b*) *Counties.*—Table VI gives similar figures for the Administrative Counties. Of the total 62 areas 19 appear to have had at least one distinct epidemic, 14 have had two or more outbreaks, and 7

TABLE VI.—ADMINISTRATIVE COUNTIES EXPERIENCING EPIDEMICS IN GIVEN YEARS
(in Brackets Observed and Expected Cases)

Essex	1926 (90, 30); 1936 (72, 17); 1937 (62, 25); 1938 (181, 50); 1945 (44, 28).
Hampshire	1928 (21, 5); 1934 (37, 7); 1938 (34, 19); 1941 (26, 13); 1944 (22, 7).
Cornwall	1919 (29, 5); 1921 (24, 4); 1941 (19, 9); 1945 (29, 7).
Westmorland ..	1922 (15, 1); 1924 (9, 1); 1937 (9, 1); 1940 (17, 2).
Lincs. Lindsey ..	1927 (17, 5); 1930 (61, 3); 1938 (37, 10); 1942 (21, 4).
Kent	1926 (86, 33); 1937 (55, 25); 1939 (80, 25); 1942 (36, 19).
Somerset	1934 (18, 6); 1940 (23, 13); 1942 (20, 8); 1944/46 (59, 22).
Hertfordshire ..	1937 (23, 9); 1941 (34, 14); 1945/46 (63, 20).
Derbyshire	1920 (23, 5); 1932 (20, 10); 1935 (27, 10).
Leicestershire ..	1926 (69, 8); 1935 (37, 5); 1938 (20, 7).
Wiltshire	1929 (19, 4); 1934 (19, 4); 1946 (18, 5).
Berkshire	1934 (20, 3); 1938 (23, 8); 1941 (56, 7).
Devonshire	1937 (33, 8); 1944 (23, 6).
Sussex E. and W. ..	1938 (73, 20); 1944 (24, 7).
Yorks. East Riding	1927 (37, 3).
Dorset	1945 (21, 5).
Buckinghamshire ..	1941 (63, 10).
Gloucestershire ..	1935 (31, 5).
Carmarthenshire ..	1938 (40, 6).

have had three, four or five outbreaks during the twenty-eight years under review, viz. Essex, Hampshire, Cornwall, Westmorland, Parts of Lindsey (Lincolnshire), Kent and Somerset. In some of these counties with repeated epidemics it would appear likely that the spread may well have been from the ports referred to in the previous table. Thus in relation to the Parts of Lindsey in Lincolnshire it may be noted that its epidemics took place in the same years as those occurring in Kingston-upon-Hull (1927), in Grimsby (1930) and in both these ports (1938). Only in 1942 does it appear alone with no obvious origin. Similarly, in 1919 and 1921 Plymouth appears in the epidemic list and it is possible that the epidemics in Cornwall emanated from here. 1934, 1938 and 1944 were epidemic years in Hampshire and there were also epidemics in Portsmouth (a very slight one in 1944). These associations in space and time between ports and hinterland are obviously suggestive though unfortunately it must be admitted that no clear distinction can be drawn between cart and horse. In other of these counties, however, there is a further suggestion of introductions from abroad. Thus in 1926 the main brunt of the Essex epidemic fell upon Grays Thurrock, situated upon the Thames. The notifications suggest a subsequent spread to Tilbury U.D. and the adjacent Orsett R.D. Concentrated mainly within a couple of months (July 17 to September 25) Grays Thurrock had some 40 cases in a population of 18,000, or an incidence of 220 per 100,000. In the October of the same year, 1926, the famous Broadstairs epidemic took place in the County of Kent. It had been preceded in August by small though sharp outbreaks in the urban districts of Sheerness and Queenborough at the mouth of the Thames.

One other point of interest may be noted in Table VI. In spite of the generally low notification rate in the Welsh counties, including Carmarthenshire, this county appears in the list with a pronounced outbreak in 1938. This would suggest again that it is not for lack of recognition of the disease and notification of cases that certain areas normally have favourably low rates of attack.

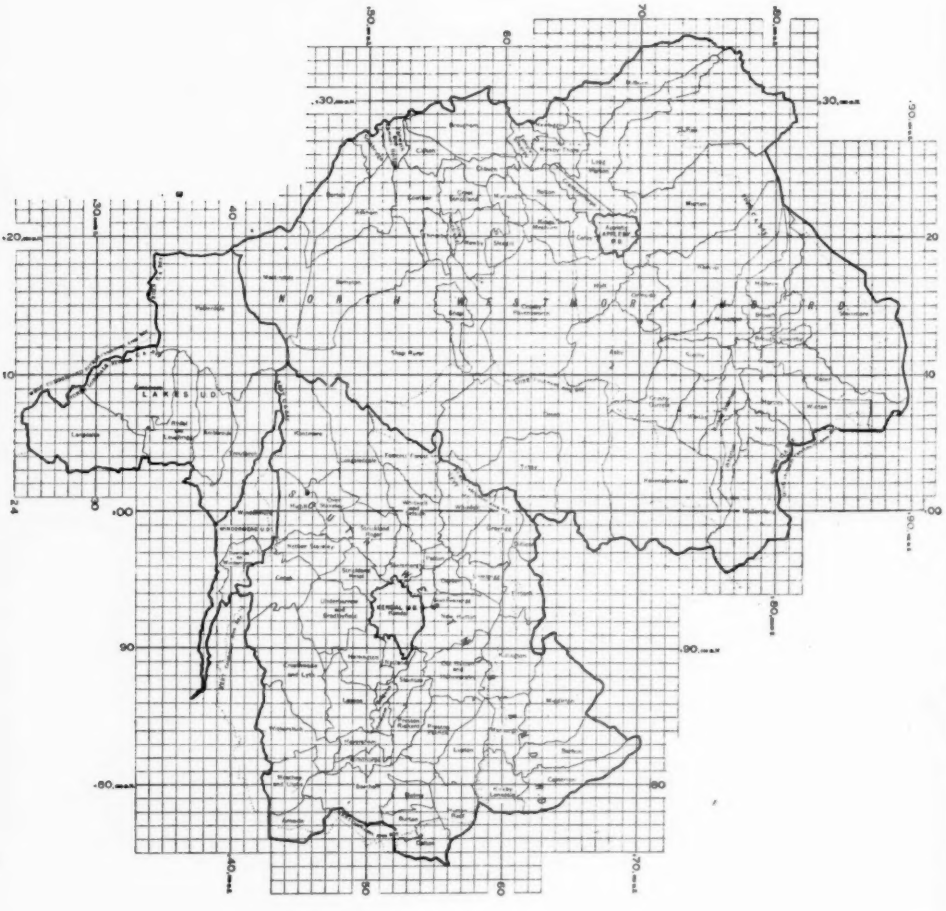
GEOGRAPHICAL VARIATIONS WITHIN COUNTIES

Administrative Counties are, of course, very large areas. In discussing the apparent localization of the disease in epidemic form, it will, therefore, be necessary to look within the county boundaries. This has already been done by Gale and Hargreaves (1953) in a most interesting study of poliomyelitis in the Counties of Devon and Cornwall over the years 1911 to 1952. They could find no direct evidence of the introduction of infection from other parts of England into these two holiday counties but they did observe a tendency for outbreaks to recur in the same rather ill-defined areas, sometimes at intervals of many years. These areas revealed no common social characteristics to which these recurrences could be attributed. I do not possess the data to allow me to study in similar close and

interesting detail the events that have taken place in other counties. I have, however, considered the distribution of notifications in space and time in a few of the counties given in Table VI and I offer these as illustrative. Whenever possible I have also consulted the relevant annual reports of the Medical Officers of Health. With changing local authority boundaries it is not easy to compute and compare the incidence over so long a period of time. The available statistics, too, often differ, though usually slightly, between weekly reports, annual reports and reports of the M.O.H. Often I must offer epidemiological impressions rather than completely accurate statistics.

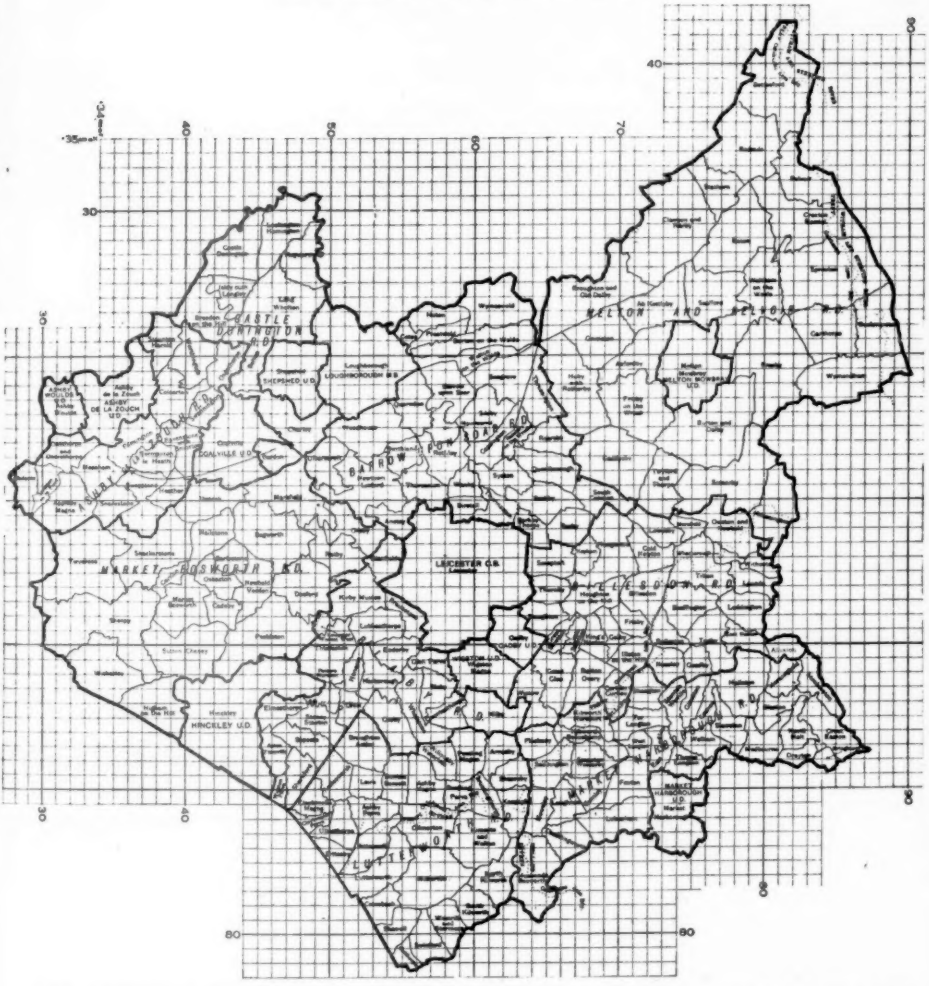
(*a*) *Westmorland.*—The County of Westmorland is particularly interesting for its small but very clear epidemic recurrences set mainly in an area notable for its relative absence of notifications. Here, there was an extremely sharp epidemic prior to the period with which I am concerned. In the report of the County Medical Officer of Health for 1922 it is said that there were outbreaks in 1910 to the seaward of the County—in Barrow-in-Furness in Lancashire, Workington, Maryport and Carlisle in Cumberland. Once again we have a possible importation by sea. In the summer and autumn of the following year, 1911, 51 cases were reported in Westmorland. They fell almost wholly in two areas, the Borough of Kendal with 22 cases and the Rural District of South Westmorland with 27 cases. Eleven years later, 1922, the same strip of South Westmorland Rural District was affected, with 10 cases; of the remaining 5 notifications in that outbreak the Borough of Kendal claimed 4. The Medical Officer of Health reports that there were 3 cases in the village of Staveley and that in that same village the 1911 outbreak began with 5 cases (Map II).

MAP II.—DIAGRAM OF WESTMORLAND



In 1924 there were three notifications very early in the year (mid-February) from West Westmorland; in the more usual autumn epidemic period 5 cases came from Kendal. In 1937 the localization was wholly different. All 9 notifications came from North Westmorland and there was an associated rise in Penrith over the Cumberland border. On the other hand the epidemic of 1940 returns to the more usual haunts with 2 cases in Kendal and 14 in South Westmorland. 11 of these were notified in one week and were, it is reported, from a privately evacuated school.

MAP III.—DIAGRAM OF LEICESTERSHIRE

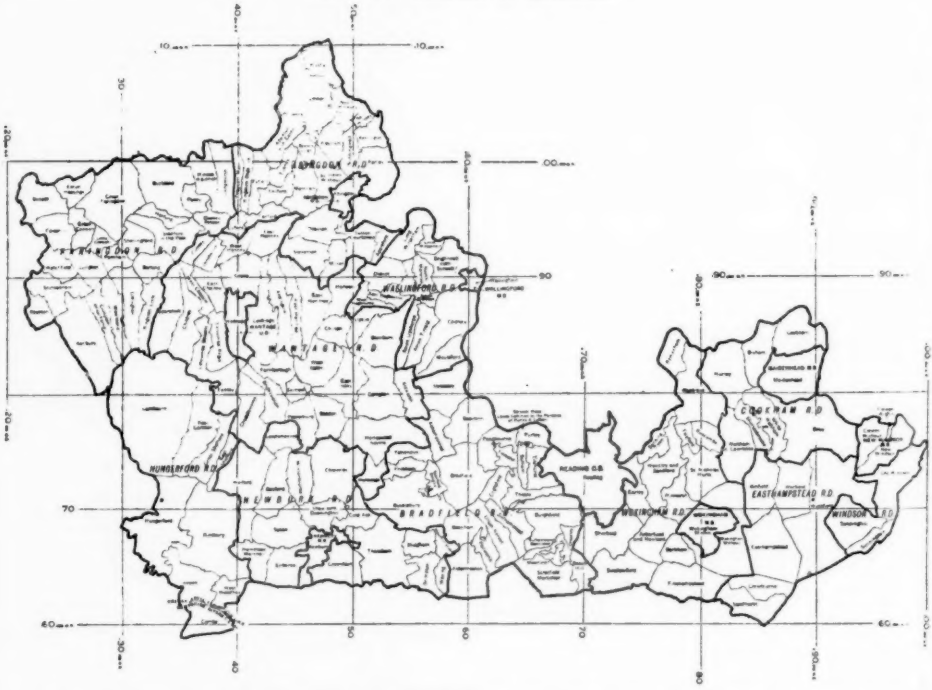


In this brief history there are two points of interest. There does appear to have been a very distinct tendency for the disease to be unduly localized in the Southern rural district of the County and in the Borough of Kendal—remembering, at the same time, that these areas contain some half of the population of the County. The second point of interest is the period of these epidemics. In 1922 most of the notifications lay in the weeks ending October 14 to November 18, in 1924 September 27 to November 1, in 1937 September 18 to November 27 and mostly after mid-October, while in 1940 11 of the 14 cases in South Westmorland were reported in the week ending November 9. We do not, of course, know the dates of onset and often notifications are long delayed. But these outbreaks do seem to show, for this country, an unduly late period of the year.

(*b*) *Leicestershire.*—Turning to the Midland areas I took for closer study the County of Leicestershire.

Here there have been three epidemics—a major outbreak in 1926 and minor outbreaks in 1935 and 1938. All three reveal a quite distinct and similar localization of cases. They have a concentration in mid-county and in its eastern parts, and an almost entire absence in the west. Thus in 1926 the areas principally affected were the Borough of Loughborough (7 cases), Barrow Rural District (17 cases), Billesdon Rural District (13), Melton Mowbray Urban District and Rural District (5 cases), Wigston Magna Urban District and Blaby Rural District (8 cases). This epidemic spread as far west as Hinckley Urban District and Rural District (13 cases) but as stated in the report of the Medical Officer of Health "a relative immunity was shown by the coal mining districts of the western part of the County" (Map III). In the smaller epidemics of 1935 and 1938 it is the same areas that appear prominently—Loughborough M.B. (4 and 1 case), Barrow R.D. (4 and 3 cases), Melton U.D. (4 and 2 cases), Billesdon R.D. (2 and 2 cases), Blaby R.D. (1 and 3 cases), Melton and Belvoir R.D. (17 and 3 cases). Except for Shepshed U.D. (1 and 4 cases) the western areas do not appear at all in these epidemic years and, indeed, over all the years 1931 to 1946 (for which figures are readily available) they have reported but a handful of cases—e.g. the Urban Districts of Coalville, Ashby de la Zouche, Ashby Woulds and Oadby. The Medical Officer of Health in his report for 1938 himself notes that these three epidemics "had a very similar distribution, most of the cases occurring in the Melton Mowbray area in each instance". Possibly, as he suggested in 1926, the disease "selects sparsely populated areas, in which acquired immunity is low, rather than populous areas, where the threshold of resistance to common infections is relatively high".

MAP IV.—DIAGRAM OF BERKSHIRE



(*c*) *Berkshire.*—On the other hand the third county whose figures I examined in more detail—Berkshire—hardly fits that hypothesis. It suffered two small outbreaks in 1934 and 1938 and a relatively severe one in 1941. The epidemic of 1934 struck the Newbury and Hungerford area (some 13 cases) and to a lesser extent Cookham, Windsor and Wokingham (9 cases). Both in 1938 and 1941 it was this more urban side of the County that was affected. There were 8 cases in Wokingham R.D. and 12 in Easthampstead R.D. in 1938. In 1941 there were 50 notifications revealing small foci in the Rural Districts of Wokingham (3), Cookham (6), Easthampstead (3), and Windsor (2), and relatively large outbreaks in New Windsor M.B. (14 cases) and Maidenhead M.B. (22 cases). Totalling the three epidemics gives 79 notifications in a population (at 1938) of about 115,000 persons in this relatively small eastern and more urbanized section of the County (Boroughs of Maidenhead, New Windsor and Wokingham; Rural Districts of Cookham, Easthampstead,

Windsor and Wokingham). On the other hand there were only 28 notifications in a population of almost identical size in the whole of the remainder of the County (Boroughs of Abingdon, Newbury and Wallingford, Urban District of Wantage, Rural Districts of Abingdon, Bradfield, Faringdon, Hungerford, Newbury, Wallingford and Wantage) (Map IV).

The tendency to recurrences in the same localities is not as striking in Berkshire as in Westmorland and Leicestershire but there are some signs that it is there. On the other hand, examination of two further counties, Wiltshire and Hampshire, gave no such suggestion. In both counties the small outbreaks appeared to be widespread and the foci that arose, such as Swindon and Aldershot, did not recur.

The Absence of Epidemics in Certain Towns and Areas

Equally striking is the complete lack of epidemics, or even a ripple on the yearly level, in certain large towns and other areas. Examples are given in Fig. 1 which relates to four selected county

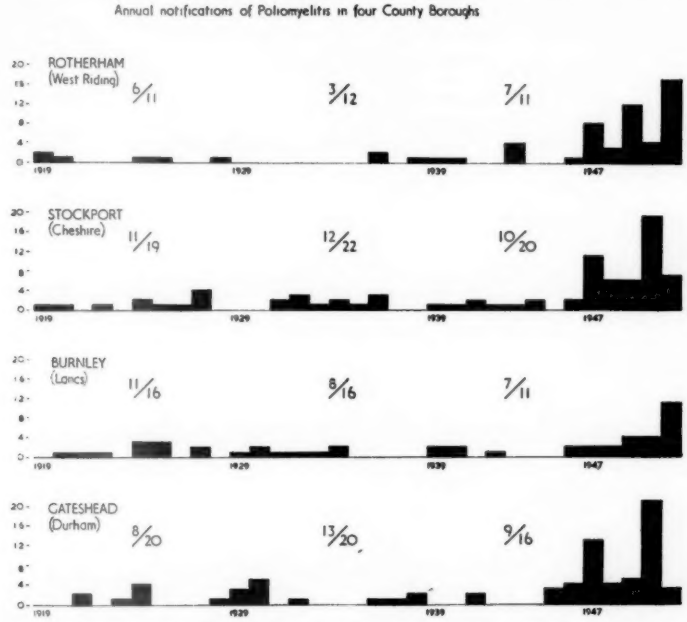


Fig. 1.—Annual notifications of poliomyelitis in four County Boroughs with observed and expected cases for specified periods.

boroughs in the Counties of Durham, Lancashire, Cheshire and the West Riding. Between 1919 and 1946 none of these towns shows any epidemic fluctuation. Annually they report no cases at all or only 2 or 3. Yet when the widespread epidemic of 1947–51 appeared they still remained but little affected. In these years each had, as Benjamin and Logan show, a level substantially and significantly below the average for the whole country. Their relative absence of cases between 1919 and 1946 would have rendered them particularly vulnerable, one might have expected, to the widespread infection of 1947. If, on the other hand, the absence of overt cases in the mid-war years implies subclinical infections and the maintenance of a high level of immunization, continuing into the post-1947 period, then the question again arises, why this should be a feature of these towns and not of many other equally densely populated towns in England and Wales? What are the characteristics that differentiate them?

The Age Incidence of Attack

At a loss to answer these questions I pass to other aspects of my subject. The changing age distribution of attack during the present century has naturally attracted much attention. There is no doubt that, in this country at least, more older persons are attacked than heretofore. Figures given by Benjamin and Gale (1949) show the following proportional distribution for reported cases in England and Wales:

Period	0–4 years	5–14 years	15 and over
1912–19	65%	28%	7%
1944–48	32%	36%	32%

The figures for 1944–48 are almost identical with those published by Logan (1952) for 1947–50 (34%, 35% and 31%). These changes are clearly far beyond what might be due merely to the changing age constitution of the population at risk (as may be shown by converting the absolute figures into rates of attack).

The figures for 1912–19 Benjamin and Gale extracted from the Annual Reports of the Medical Officer of the Local Government Board and the first report of the Chief Medical Officer of the Ministry of Health. They lament that "unfortunately there is a long period, from 1920 to 1943, for which comprehensive figures for the whole country are not available". While that statement is undoubtedly true I believe that much information, and possibly representative information, on the age distribution in these years could be gleaned from a study of the reports of Medical Officers of Health. I have not made any such general study but I have consulted the local reports for all the areas in which in any given year there has been some epidemic spread. Most of these reports give age particulars of the notifications. Clearly epidemic areas may not be representative and might well have an unusual age incidence; but in fact the figures I have compiled for such county boroughs are not very dissimilar from those given for the whole country in 1912–19 by Benjamin and Gale (*see* Table VII). Their figures were 65, 28 and 7%; for half a dozen county boroughs in 1919–23 I have

TABLE VII.—THE AGE DISTRIBUTION OF NOTIFIED CASES IN DIFFERENT PERIODS OF TIME

Age	County Boroughs										Administrative Counties					
in	1919–23		1924–26		1927–30		1931–37		1938		1919–28		1929–37		1938	
years	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0–4	140	*70*	147	*74*	136	*67*	145	*66*	85	*39*	41	*40*	64	*39*	21	*37*
5–14	49	*24*	39	*19*	52	*25*	58	*26*	92	*42*	48	*46*	74	*45*	25	*45*
15+	13	*6*	15	*7*	16	*8*	17	*8*	41	*19*	15	*14*	26	*16*	10	*18*
Total	202	*100*	201	*100*	204	*100*	220	*100*	218	*100*	104	*100*	164	*100*	56	*100*

The areas involved are:

County Boroughs:

1919–23 Bristol, Oxford, Plymouth, Birmingham, Liverpool, Cardiff.
1924–26 Sheffield, Walsall, Cardiff, Nottingham, Leicester.
1927–30 Leeds, Kingston-upon-Hull, Liverpool, Bristol, Grimsby.
1931–37 Sheffield, Liverpool, Kingston-upon-Hull, Wigan, St. Helens, Portsmouth, Exeter, Manchester, Gt. Yarmouth, West Ham.
1938 Ipswich, Swansea, Reading, Grimsby, Bristol, Portsmouth, Kingston-upon-Hull, Cardiff, Oxford.

Administrative Counties:

1919–28 Westmorland, Rutland, Leicester.
1929–37 Lancashire, Devon, Leicester.
1938 Carmarthen, Leicester.

70, 24 and 6%. The interesting point of the table is the relative lack of change between 1919–23 and 1931–37—possibly a slight increase in the proportion of older persons attacked but certainly very slight. In 1938, when England and Wales experienced its sharpest epidemic up to that time, there was, however, a decided break. A much greater proportion of the notifications fell at school ages and beyond. This change persisted in 1939–46 and in the widespread epidemics of 1947 and subsequently it has become still more marked. Again age changes in the population at risk can play but a small part. Conceivably, however, it might be due merely to the fact that I am considering different groups of county boroughs in these years. I have, therefore, limited the comparisons to four towns which experienced epidemics both in earlier years and in 1938 (*see* Table VIII). The same picture still emerges. On the other hand some few figures available from county records reveal a much higher age distribution than that of the towns from 1919 onwards; and they show no such change in 1938 (*see* Table VII).

TABLE VIII.—THE AGE DISTRIBUTION OF NOTIFIED CASES IN FOUR COUNTY BOROUGHS*

	1919–33		1938	
Age in years	No.	%	No.	%
0–4	198	*66*	49	*46*
5–14	77	*26*	35	*32*
15+	25	*8*	26	*22*
Total	300	*100*	110	*100*

*The County Boroughs and the years involved are:
Bristol, 1919, 1921, 1929, 1938.
Oxford, 1919, 1938.
Cardiff, 1923, 1924, 1938.
Kingston-upon-Hull, 1927, 1933, 1938.

A similar time study was made by Benjamin and Gale for the County of London and revealed

a significant rise in the average age of attack "after the middle of the 1930s". The change appears to have started there in 1933–35 but to have become much more pronounced in 1936–38. I would agree with them that it is unlikely that such a movement can be accounted for by increased reporting of abortive cases. In the county boroughs studied here it seems to have been remarkably abrupt. Perhaps the 1938 epidemic was due to a new strain of virus against which the city populations had acquired no immunity in early life.

Sites of Paralysis

For a few of these epidemics it is also possible to extract the sites of paralysis from the reports of the local Medical Officers of Health. From Cardiff (1923), Birmingham (1923), Kingston-upon-Hull (1933) and Manchester (1936) there are 150 such cases of which 74% were children under the age of 5. Between them they had 223 recorded sites of paralysis in upper and lower limbs and a ratio of 1 upper limb to 3·2 lower limbs. In the children under 5 reported upon by Bradford Hill and Knowelden (1950)—excluding those who had been inoculated within a month of their illness—the ratio in 424 sites was 1 upper limb to 2·3 lower limbs. The difference between the two ratios might well be due to chance (P is approximately 0·10). In other words there is no significant evidence of a general change in the arm/leg ratio with the greatly increased incidence of inoculations that has occurred since 1942. The effect of inoculations again appears to be limited to those recently carried out.

Summary and Conclusion

Finally, for all these major and minor epidemics in England and Wales between the wars I studied the reports of the Medical Officers of Health (I am indebted to many who sent or lent me these early reports). It seemed just possible that seen *en masse* and in retrospect at this later date some epidemiological feature might stand out. There was none that I could detect. Many give fascinating accounts of these outbreaks but they are, perhaps, more striking in their variety than in their resemblance. Thus I am left with wholly unresolved questions.

If it be true that fresh introductions of poliomyelitis were quite frequently taking place through the ports why was the spread so limited at this time? Some of these epidemics were on no mean scale—for example those in Grimsby and Kingston-upon-Hull. Yet they did not seem to travel far or wide in epidemic form but on the whole to stay in the town and closely adjacent counties. Similarly a county epidemic would often appear to be limited to that county or contiguous areas. This would seem to conform rather to the present conception of the disease as following relatively narrow channels of dissemination through immediate contacts than to the more generally held view of a widely dispersed virus infecting nearly all the people of an area. It might, perhaps, be argued that dissemination was widespread but in a subclinical form. The fact then that the disease appeared clinically and epidemically over a circumscribed area but no less widely but yet subclinically over a more distant area would clearly call for explanation.

Secondly there is the question of the changes in age of incidence. It has long been noted that "infantile paralysis" has ceased to be predominantly infantile (or indeed paralytic). There has been, it has been maintained, a gradual shift to an older age distribution in countries with improving standards of hygiene. The explanation put forward is lack of immunization in childhood with the subsequent exposure to risk of non-immunes at school ages and in adult life. Yet, however that may be, in the towns of England and Wales for which I have been able to offer figures there may also, it seems, have been quite an abrupt change in, or near to, the widespread epidemic of 1938. Did a new strain of virus find lodgment about that date, and are we suffering from yet another in the epidemics since 1947?

Lastly there is the main question from which I set out. Why do certain cities experience repeated outbreaks whereas others report none though they would appear to be no more or no less vulnerable in terms of overcrowding and hygienic standards? Why does the disease tend to reappear in certain localities? If the phenomena of 1947 were due to a new strain of virus one might at least expect it to strike equally at cities whose past experience had been good or ill. Yet in the main it seems to have fallen more heavily upon those areas of England and Wales which had had a similar unfavourable experience of poliomyelitis in 1919–46, less heavily upon those with a favourable history. What are the barriers and facilities offered in these respective areas? The records of the General Register Office can, I suspect, take us no farther and there would seem to be scope for field studies.

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APPENDIX

The Ratio of Observed to Expected Cases (Percentages) in County and County Borough Areas in Specific Periods

(Ratios in italics are significantly low
Ratios in bold type are significantly high)

Region and Area	1947-1950	1939-1946	1929-1938	1919-1928	1919-1946
NORTHERN					
Cumberland A.C.	109	82	69	111	88
Carlisle C.B.	*62*	74	52	35	*54*
Durham A.C.	92	*45*	*46*	*52*	*48*
Darlington C.B.	*26*	60	73	112	80
Gateshead C.B.	*68*	57	65	*41*	*55*
South Shields C.B.	88	77	*48*	86	*69*
Sunderland C.B.	94	*52*	117	*36*	*72*
West Hartlepool C.B.	*48*	42	78	102	75
Northumberland A.C.	93	*64*	*52*	*58*	*57*
Newcastle-on-Tyne C.B.	**126**	*38*	117	106	89
Tynemouth C.B.	74	*23*	81	*30*	*47*
Westmorland A.C.	119	**350**	**163**	**309**	**273**
Yorkshire North R.A.C.	90	107	100	74	94
Middlesbrough C.B.	*64*	*36*	103	*25*	*57*
E. & W. RIDINGS					
Yorkshire East R.A.C.	88	*53*	126	**192**	122
Kingston-upon-Hull C.B.	*80*	85	**197**	**296**	**200**
Yorkshire West R.A.C.	105	111	*73*	*68*	*83*
Barnsley C.B.	**173**	102	67	146	103
Bradford C.B.	96	*42*	*25*	*63*	*43*
Dewsbury C.B.	118	137	*0*	*0*	*40*
Doncaster C.B.	78	*28*	44	—	*36*
Halifax C.B.	*33*	80	112	*33*	76
Huddersfield C.B.	83	78	*51*	99	75
Leeds C.B.	103	*66*	*37*	*55*	*50*
Rotherham C.B.	*71*	62	*25*	54	*47*
Sheffield C.B.	105	77	**154**	**183**	**140**
Wakefield C.B.	95	96	51	*0*	*50*
York C.B.	**183**	**193**	139	78	**140**
NORTH WESTERN					
Cheshire A.C.	*81*	*74*	*69*	92	*77*
Birkenhead C.B.	*70*	*46*	*57*	*51*	*51*
Chester C.B.	83	90	127	109	111
Stockport C.B.	*49*	*51*	*55*	*57*	*54*
Wallasey C.B.	*48*	*40*	*50*	*42*	*44*
Lancashire A.C.	*75*	*86*	*84*	*65*	*79*
Barrow C.B.	88	50	*28*	*0*	*25*
Blackburn C.B.	*28*	82	*50*	*36*	*54*
Blackpool C.B.	*39*	*37*	*32*	89	*47*
Bolton C.B.	*60*	93	*59*	*47*	*65*
Bootle C.B.	*59*	56	78	87	76
Burnley C.B.	*22*	64	51	70	*62*
Bury C.B.	*49*	75	*21*	57	*50*
Liverpool C.B.	*88*	*48*	*74*	86	*71*
Manchester C.B.	**114**	108	*76*	*74*	*84*
Oldham C.B.	*43*	58	*27*	*32*	*37*
Preston C.B.	*43*	**160**	*46*	*53*	82
Rochdale C.B.	*63*	*31*	78	56	*57*
St. Helens C.B.	*37*	92	**149**	*42*	96
Salford C.B.	**159**	69	*34*	*40*	*45*
Southport C.B.	*28*	92	91	87	89
Warrington C.B.	72	54	107	83	83
Wigan C.B.	*61*	*25*	107	*36*	*58*
NORTH MIDLAND					
Derbyshire A.C.	*58*	77	**131**	**124**	111
Derby C.B.	*63*	72	107	87	90
Leicestershire A.C.	88	83	**196**	**238**	**169**
Leicester C.B.	**165**	70	**132**	**303**	**165**
Lincs. Holland A.C.	**155**	57	95	114	88
„ Kesteven A.C.	**218**	**157**	124	**178**	**152**
„ Lindsey A.C.	**125**	**171**	**284**	**145**	**165**
Grimsby C.B.	**159**	124	**409**	*38*	**202**
Lincoln C.B.	100	**344**	47	100	**160**
Northamptonshire A.C.	**117**	*61*	**144**	109	105
Northampton C.B.	88	*46*	113	119	93
Nottinghamshire A.C.	*82*	96	*75*	*56*	*77*
Nottingham C.B.	*74*	*55*	*46*	**144**	*80*
Peterborough A.C.	93	70	34	41	*48*
Rutland A.C.	138	0	**413**	**621**	**375**
MIDLAND					
Herefordshire A.C.	**148**	**181**	**159**	145	**161**
Shropshire A.C.	*73*	**134**	103	130	**122**
Staffordshire A.C.	94	105	*68*	88	*87*
Burton-on-Trent C.B.	*61*	145	63	**224**	**145**
Smethwick C.B.	102	131	80	67	92
Stoke-on-Trent C.B.	*50*	*23*	*55*	94	*58*
Walsall C.B.	83	58	63	**157**	92
W. Bromwich C.B.	*44*	42	*29*	92	*54*

Region and Area	1947-1950	1939-1946	1929-1938	1919-1928	1919-1946
MIDLAND—*continued*					
Wolverhampton C.B.	105	**269**	61	*47*	122
Warwickshire A.C.	**122**	**156**	100	**149**	**134**
Birmingham C.B.	**151**	104	*62*	**125**	95
Coventry C.B.	93	105	*35*	108	80
Worcestershire A.C.	110	87	84	94	88
Dudley C.B.	**203**	101	40	*0*	*46*
Worcester C.B.	110	136	47	78	88
EAST					
Bedfordshire A.C.	**127**	108	*63*	74	83
Cambridgeshire A.C.	*52*	109	67	**101**	91
Isle of Ely A.C.	*37*	48	*37*	43	*42*
Hertfordshire A.C.	101	**159**	101	98	**123**
Huntingdonshire A.C.	80	76	160	143	126
Norfolk A.C.	**116**	99	86	100	95
Great Yarmouth C.B.	94	57	141	112	113
Norwich C.B.	**128**	98	*48*	*37*	*59*
East Suffolk A.C.	*80*	126	84	101	102
Ipswich C.B.	*27*	68	**172**	116	122
West Suffolk A.C.	*73*	86	**172**	114	126
LONDON & S. EASTERN					
Essex A.C.	99	*74*	**207**	**141**	**143**
East Ham C.B.	*57*	68	151	*53*	93
West Ham C.B.	*51*	*35*	127	*52*	*78*
Southend-on-Sea C.B.	81	149	93	**193**	**137**
Kent A.C.	**112**	**121**	107	115	**114**
Canterbury C.B.	81	**437**	121	135	**218**
London A.C.	**128**	*81*	106	106	101
Middlesex A.C.	99	**116**	111	109	**112**
Surrey A.C.	102	105	97	**119**	105
Croydon C.B.	92	79	83	75	*79*
East Sussex A.C.	93	96	**136**	83	107
Brighton C.B.	94	144	102	**150**	**130**
Eastbourne C.B.	*36*	100	*11*	94	63
Hastings C.B.	88	27	67	**225**	111
West Sussex A.C.	89	**150**	**173**	108	**147**
SOUTHERN					
Berkshire A.C.	109	**262**	**185**	118	**194**
Reading C.B.	88	**171**	**209**	55	**147**
Buckinghamshire A.C.	*85*	**235**	69	73	**135**
Dorsetshire A.C.	**172**	**186**	125	131	**146**
Oxfordshire A.C.	84	**146**	**229**	**171**	**180**
Oxford C.B.	90	**282**	**354**	**259**	**301**
Southampton A.C.	104	**177**	**132**	**132**	**147**
Bournemouth C.B.	98	100	96	97	98
Portsmouth C.B.	*66*	89	**138**	*54*	96
Southampton C.B.	**122**	111	78	77	87
Isle of Wight A.C.	**239**	74	**239**	83	**135**
SOUTH WESTERN					
Cornwall A.C.	**132**	**141**	*46*	**152**	112
Devonshire A.C.	**119**	**103**	**128**	92	108
Exeter C.B.	108	120	142	70	116
Plymouth C.B.	*59*	97	*46*	**213**	118
Gloucestershire A.C.	106	89	**128**	80	99
Bristol C.B.	**228**	*66*	118	**173**	**119**
Gloucester C.B.	*59*	*21*	66	*0*	30
Somersetshire A.C.	**117**	**190**	**140**	114	**149**
Bath C.B.	118	132	122	94	118
Wiltshire A.C.	**121**	**151**	**167**	104	**142**
WALES					
Anglesey A.C.	*26*	*14*	*13*	38	*22*
Brecknock A.C.	79	127	56	76	85
Caernarvon A.C.	*63*	115	61	76	84
Cardigan A.C.	*44*	38	77	101	73
Carmarthen A.C.	106	*47*	**161**	*40*	85
Denbigh A.C.	87	96	81	79	85
Flint A.C.	100	79	*42*	93	*70*
Glamorgan A.C.	*73*	110	*49*	*61*	*70*
Cardiff C.B.	103	**212**	111	**278**	**198**
Merthyr Tydfil C.B.	*58*	33	*27*	**360**	**155**
Swansea C.B.	113	*50*	**254**	*48*	**124**
Merioneth A.C.	*76*	*16*	60	31	*37*
Monmouth A.C.	*49*	79	*42*	*49*	*56*
Newport C.B.	*39*	63	114	122	100
Montgomery A.C.	**148**	145	143	51	114
Pembroke A.C.	*47*	62	*21*	64	*49*
Radnor A.C.	**154**	**375**	171	90	**210**

Section of Urology

President—HUGH DONOVAN, M.B., F.R.C.S., F.R.C.S.Ed.

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Hyaluronidase and Urinary Stone

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BUTT *et al.* (1952) suggest that, of the many factors affecting stone formation in the urinary tract, the concentration of colloidal matter in the urine is one of the most important. Von Hemsbach, in 1856, first put forward this hypothesis stating that two factors were necessary for the production of calculous material: firstly an organic compound of mucous character in which insoluble and poorly soluble materials could be deposited and, secondly, a fluid supersaturated with petrifying or encrusting agents. Since this statement, relatively little has been added to our knowledge of the former factor. Butt, however, has brought this theory once again into prominence. Clinically, the proof of the hypothesis lies in a study of various ethnic groups. Butt and his co-workers have found that in those groups in which stone formation is uncommon, there is a high concentration of colloid in the urine, this concentration being measured by the electron microscope and surface tension. They have suggested that the surface tension of urine in the male is lower than in the female, with a corresponding increase in the incidence of stone in the male sex. In order to prevent or retard stone formation, they have used the enzyme hyaluronidase: in their various papers they have postulated several different modes of activity of the enzyme but in the main they suggest that the substrate of the enzyme, i.e. hyaluronic acid, is excreted in the urine with corresponding depression of the surface tension, or that one of the breakdown products, acetyl glucosamine or glucuronic acid is excreted.

The influence of hyaluronidase on these several factors has been reinvestigated:

(1) The surface tension of many urines has been determined by the drop weight method and the influence of hyaluronidase on this physical factor investigated.

(2) The acetyl glucosamine level in the urine has been determined following increasing doses of the enzyme.

(3) Vesical calculi have been induced in the rat bladder by the implantation of zinc pellets, daily injections of hyaluronidase (500 Turbidity Reducing Units) being given to half the series.

Investigation of surface tension revealed the following facts:

The surface tension of human urine is related directly to the specific gravity—the higher the specific gravity the lower the surface tension (Fig. 1).

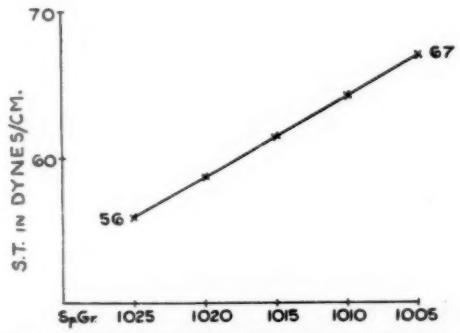

FIG. 1.—The relationship between surface tension and specific gravity in a normal male aged 31.

The surface tensions of male and female urine, when correlated with the specific gravity of the urine, do not differ significantly. Thirty individuals were examined repeatedly (Fig. 2).

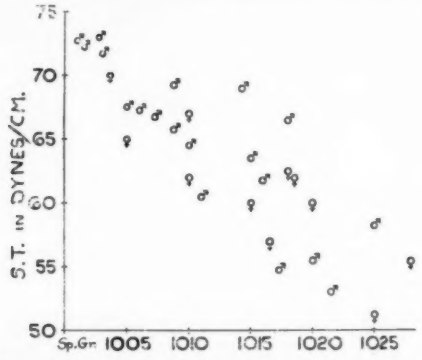

FIG. 2.—The relationship between surface tension and specific gravity in 30 patients with normal kidneys.

If hyaluronidase is injected, no alteration in surface tension occurs. Fig. 3 demonstrates this in two cases, one male and one female.

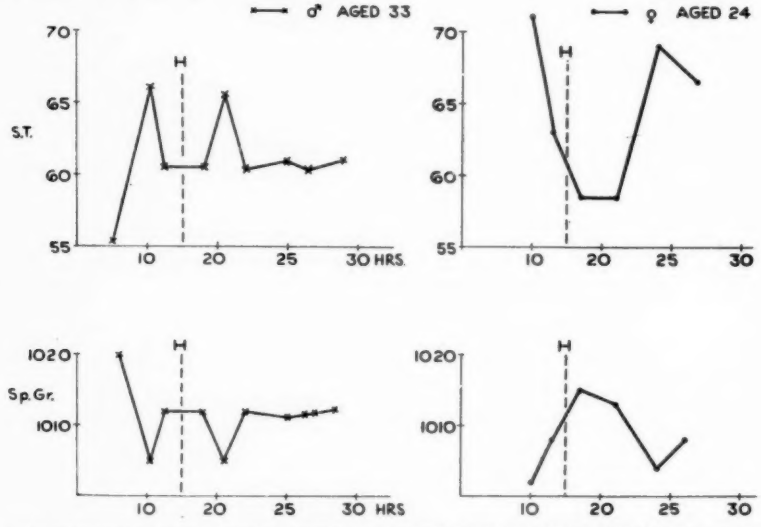

FIG. 3.—The relationship between surface tension and specific gravity (500 T.R.U.) showing no depression of surface tension following injections of hyaluronidase. H marks the injection time.

The acetyl glucosamine content of human urine is for all practical purposes negligible, approximately one part in one million. Four individuals were given increasing doses of this enzyme—the investigation commenced with injections of 500 T.R.U. and ended with doses of 5,000 T.R.U. No increase in the acetyl glucosamine level was demonstrated. It had been hoped to pursue this investigation further by the estimation of glucuronic acid levels but very variable quantities of this substance are normally excreted each day making correlation between injection and concentration difficult to assess.

The results of the induced vesical calculi in rats suggested that no profound influence was exerted by hyaluronidase. The control rats (20) developed a total weight of calculous material equal to 2,050 mg. whilst the rats (20) in the injected series developed a total weight of 2,271 mg. The rats in the control series were killed after 80 days whilst in the series injected only 60 days were allowed for the development of calculi. This might suggest that hyaluronidase, far from retarding stone formation,

actually enhances the production of magnesium ammonium phosphate hexahydrate in the rat. That the zinc does not inhibit any action which hyaluronidase may exert on calculus formation is proved by the fact that no zinc is found in the stones even in those layers in closest contact with the pellet.

In view of these results, it was considered very doubtful whether the work of Butt *et al.* (1952) would be substantiated in clinical practice. It was decided to await the results of further clinical trials by other centres before embarking on this method of therapy.

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The Influence of Hyaluronidase in Renal Lithiasis

By A. G. DINGLEY, M.Chir., F.R.C.S., and A. W. BADENOCH, M.D., Ch.M., F.R.C.S.
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THE possible value of hyaluronidase in the treatment of renal lithiasis was first pointed out by Butt *et al.* (1952). Having found that an injection of hyaluronidase cleared the urine in patients who previously had a turbid urine they postulated that a hyaluronidase substrate was probably a normal component of urine, and that this was responsible for maintenance of the normal colloid-crystalloid balance. An upset of this balance was probably an important factor in the production of urinary calculi, and this could be corrected by the administration of hyaluronidase, which increased the amount of protective colloid in the urine.

Butt reported 24 cases of renal stone which had been followed for periods of eleven to twenty-one months. On hyaluronidase therapy, 19 of these cases showed no new stone formation and no increase in size of existing stones, and in 4 cases there was actual diminution in the size of stones already present.

Encouraged by these results, we therefore decided that we would give the administration of hyaluronidase a trial in certain cases of lithiasis, either prophylactically or as a definitive treatment, and we have now given it in 8 cases of renal stone which we considered suitable. It is on these cases that this communication is based.

For various reasons we considered them unsuitable for surgical intervention and hoped that some might be influenced by the administration of hyaluronidase.

Case I.—A fit man of 36, who three months previously had had a small stone removed from the upper calyx of his right kidney, and then presented again with further symptoms of severe loin pain and hæmaturia. X-ray showed a single small calculus in the middle calyx of the right kidney.

In view of the small size of the calculus and the probable difficulty of the operation, it was decided to give the patient a course of hyaluronidase in the hope of alleviating his symptoms. He was therefore given daily subcutaneous injections of 1,000 units of hyaluronidase for three months, but throughout this time his symptoms continued and, in fact, became more severe, necessitating surgical treatment. An X-ray taken immediately before operation showed the calculus to be virtually unaltered in size, or, if anything, very slightly larger than before.

Case II.—Male aged 43, who fifteen years previously had had a right nephrectomy for stone, and eight months previously a pyelolithotomy for a staghorn calculus on the left side. He was now complaining of an aching pain in the left loin and X-ray showed two small opacities in the lower calyx of the left kidney.

Since these were small stones in a solitary kidney which had already been operated upon recently, hyaluronidase treatment was tried. Daily injections of 1,000 units were started and given over a period of nine months. During this treatment his symptoms, which had never really been severe, were unaltered but repeated X-rays showed gradual increase in size of the calculi. The final X-ray after nine months' treatment showed a considerable increase in size of the calculi and yet during the whole course of treatment he had maintained a high fluid intake and output.

Case III.—A male aged 64, who suffered from severe chronic bronchitis and emphysema. Twenty years previously he had had bilateral nephrolithotomy performed and had had symptoms of recurrent stones for ten years. His main complaint was of hæmaturia, with occasional episodes of recurrent infection, but there was little pain. X-ray showed multiple bilateral renal calculi.

It was decided that because of the scattered situation of the stones and his poor physical condition, operative treatment was out of the question. He was started on a course of hyaluronidase injections of 1,000 units every other day, and continued this treatment for nine months. During the course of treatment his pre-existing hypertension became worse and latterly he developed renal failure, was admitted to hospital and died within a month.

An X-ray taken shortly before death showed a slight increase in size of the calculi, and a "fanning-out" of those in the left kidney, presumably due to hydronephrosis.

Case IV.—A male aged 58, who had had a right nephrectomy for stone thirty-five years ago, a left ureterolithotomy twenty-three years ago and a left pyelolithotomy eight years ago. A further stone formed in the lower pole of the left kidney six years ago. An X-ray taken in July 1953 showed three stones in the left kidney, each in a minor calyx, without much dilatation and with fairly good renal function. There had been little change in the size of the stone in the lower calyx over the last six years. He had recently spent

three months in a mental hospital and on account of this and his physical condition further surgical treatment was considered inadvisable. He was, however, having attacks of pain and was therefore put on hyaluronidase.

He was given 100 daily subcutaneous injections of 1,000 units of hyaluronidase and his backache was much improved. The final X-ray, however, showed that there is marked increase in size of the lower stone, and this increase has taken place while the patient has been on hyaluronidase (Figs. 1 and 2).

FIG. 1 (*Case IV*).—Plain X-ray showing stone in lower calyx which had scarcely increased in size over a period of six years.

FIG. 2 (*Case IV*).—X-ray taken six months later, after 100 injections of hyaluronidase.

Case V.—Male aged 44, who was X-rayed after having passed a small stone, was found to have a further stone in the right kidney and some gravel in the left.

He was given a course of 40 injections of hyaluronidase on alternate days, and the final X-ray showed no change in the size of the calculi.

Case VI.—A male aged 43, was first seen in an attack of right renal colic. X-ray at this time showed a stone obstructing the right ureter together with gravel in the lower poles of both kidneys. He was a diabetic requiring insulin injections. Following ureterolithotomy the diabetes improved sufficiently to obviate the need for insulin.

He was started on hyaluronidase and given a total of 155 injections of 1,000 units on alternate days. During the treatment he passed a small stone from the left kidney (during which time incidentally he had glycosuria for three days), but the final X-ray after six months showed no other change.

Case VII.—A man of 44, who, after an attack of left renal colic, was found to have a stone in the upper third of the left ureter together with a stone in each kidney. A left ureterolithotomy was performed but he had a further attack of pain on the left side six weeks later when the renal stone was found to have moved into the ureter. Some gravel was seen in the left kidney. A further X-ray on admission to hospital showed that the ureteric stone had disappeared although there was no evidence of his having passed it.

In view of the presence of another stone in the right kidney and gravel in the left, he was given a five-month course of hyaluronidase injections on alternate days. Re-examination after this treatment showed a further stone obstructing the lower third of the left ureter, but otherwise the X-ray appearances were unaltered.

Case VIII.—An ex-Serviceman of 33, who since 1939 had had 9 operations for recurrent renal calculi—4 on the left and 5 on the right. He had been in fair health, although he had a severe degree of hypertension, until one month previously when he developed attacks of severe right-sided renal and ureteric colic with hæmaturia. Examination of the urine showed large quantities of amorphous debris with pus and red cells, but careful examination which included intravenous and retrograde pyelograms failed to show any evidence of stone. It was thought that his colic was due to the passage of debris, and as hyaluronidase was known to be capable of reducing the turbidity of urine in certain cases it was thought it might be useful here.

Daily hyaluronidase injections were given over a period of four months. During this treatment, the urine showed no alteration and repeated X-rays failed to show any stone formation, but there was no symptomatic relief whatsoever, in fact the attacks of colic became more severe. A ureteric catheter was passed and the renal pelvis washed out with Suby's solution. This gave immediate relief of symptoms which lasted for approximately one month.

Three months later he was readmitted to hospital with gross hypertension and renal failure from which he died within a few days.

Post-mortem examination showed the kidneys to contain much soft chalky material but no actual stones were found.

Conclusions

Although our series of 8 cases is small we feel that it is reasonable to draw some conclusions and to compare our results with those reported by Butt *et al.* (1952). In 19 of their 24 cases on hyaluronidase therapy there was no new stone formation, and no increase in size of existing stones, and in 4 cases there was actual diminution in size of existing stones.

While maintaining a high fluid intake and output and while receiving a comparable dosage of hyaluronidase, only 3 of our 8 cases showed no new stone formation. 4 showed an actual increase in size of existing stones, and in 2 of these cases the stones lay in a solitary kidney. In none of our cases was there any diminution in size of an existing stone.

In the case of the young man with phosphatic debris causing severe colic, we were most hopeful of obtaining at least some symptomatic relief, but hyaluronidase seemed to have no beneficial effect whatsoever. In fact, the only case in which there was relief of symptoms showed a marked increase in size of the renal stone during treatment, and presumably it was the fixation of this stone which gave him that relief.

Two of our cases died while receiving hyaluronidase but in neither case was death in any way thought to be attributable to the effects of this treatment.

Our results, therefore, have been disappointing and we have been led to believe that the administration of hyaluronidase has no material effect upon the natural history of urinary stone. In view of the necessity for a long-continued course of frequent injections this treatment does not appear to be justified by the results.

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Professor V. W. Dix, Mr. H. G. Hanley, Mr. Richard A. Mogg and Mr. F. G. Smiddy took part in the subsequent discussion.

SYMPOSIUM ON VASOTOMY

Mr. Basil H. Page (North Middlesex Hospital): *Vasotomy and the Sheath of the Vas.*

It is generally held that epididymitis after prostatectomy is caused solely by infection travelling along the lumen of the vas. If this is indeed the only route by which infection reaches the epididymis then in the operation of vasotomy only the vas itself need be divided. Although this view is generally

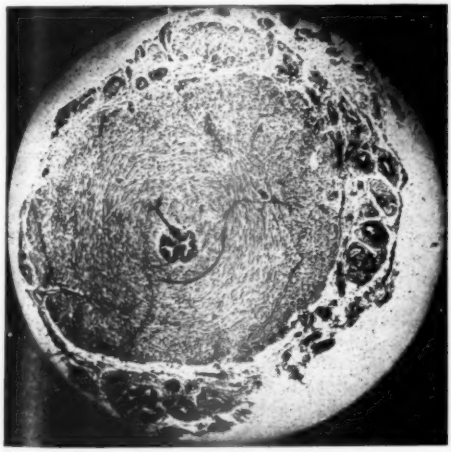

Fig. 1.

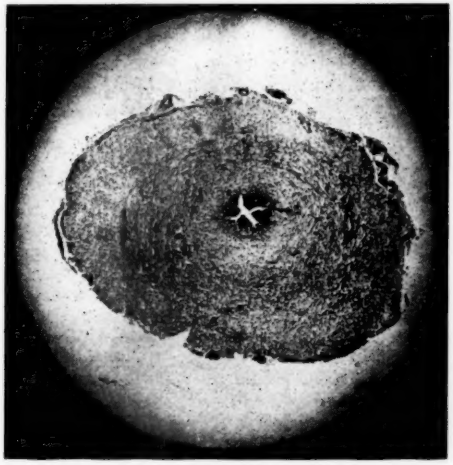

Fig. 2.

Figs. 1 and 2.—Sections of the piece of the vas excised at vasotomy. Fig. 1 shows the vas in its sheath (operation on right side), and Fig. 2 the naked vas (operation on left side).

accepted there are those who hold other views or admit other possibilities and it is often advised that the sheath of the vas should be divided as well as the vas itself (Schmidt and Hinman, 1950; Abeshouse and Lerman, 1950). I remember hearing the same view expressed by a British urologist also about 1950. The matter has some importance both theoretical and practical. In its theoretical aspect it involves a consideration of the ætiology of epididymitis, in so far as this concerns the route

by which infection reaches the epididymis. Apart from the lumen of the vas there are four possible routes, namely the blood stream, the lymphatics round the vas, the sheath of the vas, and direct spread by means of a continuous vasitis.

Although the blood-stream hypothesis has been generally discarded some experimental work on guinea-pigs by Böhm (1951) suggests that it may be important in some circumstances. On the whole the lymphatic pathway has been rejected on good grounds, chiefly anatomical. Direct spread in the tissues of the vas itself seems to play an unimportant part in causing epididymitis (Richard, 1928). The vas is surrounded by a sheath and in 1925 Rolnick reported 5 cases of inflammation of the scrotal contents which he considered was due to spread along the space between the vas and this sheath. None of the cases had a true epididymitis but rather a cellulitis spreading round the upper part of the testis and epididymis. The evidence in favour of spread of infection along the lumen of the vas to the epididymis is well established.

In order to try to evaluate the part played by the sheath of the vas in transmitting infection after prostatectomy I divided the vas differently on the two sides in a series of prostatectomy cases. On the right side the vas was divided in its sheath so that the lumen of the vas and the space between the vas and its sheath were both interrupted (Fig. 1). Whereas on the left side the vas alone was divided after opening the sheath and picking the vas out of it (Fig. 2).

TABLE I.—INFLAMMATION AT OR ABOVE VASOTOMY SITE

Patient	Right side. Vas and sheath interrupted	Left side. Vas alone interrupted
G. W. W.		Funiculitis down to vasotomy site
W. E. W.		Inflammation at vasotomy site
F. J. S.	Inflammation at vasotomy site	
J. D.	Funiculitis and vasotomy abscess: epididymis normal	
H. E.		Funiculitis at vasotomy site
W. A. W.		Inflammation at vasotomy site

TABLE II.—INFLAMMATION BELOW VASOTOMY SITE

Patient	Right side. Vas and sheath interrupted	Left side. Vas only interrupted
H. J. R. B.	Acute epididymitis	
A. J. W.		Acute epididymitis
R. H. W.	Cellulitis at and below vasotomy site	Lower pole of epididymis slightly enlarged but hardly tender
P. W.	Elastic enlargement of lower pole of epididymis	Elastic enlargement of lower pole of epididymis
H. C. L.		Firm enlargement of lower pole of epididymis
A. K.	Slight enlargement of lower pole of epididymis	Slight enlargement of lower pole of epididymis
C. B.	Slight tenderness of epididymis	
E. T. R.	Slight enlargement and tenderness of epididymis	Slight enlargement and tenderness of epididymis

There were 157 cases in the series in which this differential vasotomy was done. 14 cases out of the 157 developed some sort of inflammatory trouble in the scrotum. In 6 of these (Table I) the inflammation was at or above the site of the vasotomy and could not therefore have been influenced by the type of vasotomy. In 8 cases (Table II) there was inflammation below the vasotomy site. 5 of these had no symptoms but were found to have slight enlargement or tenderness of the epididymis and both sides were equally affected. In only 3 cases had troublesome infection apparently broken through the barrier of the vasotomy. In one of these there was a cellulitis at and below the vasotomy site and this occurred on the right side where the sheath of the vas had been interrupted as well as the vas itself. There were 2 cases of acute epididymitis: one was on the right side and one on the left, so that both types of vasotomy had been equally ineffective. Both these cases had had previous catheter drainage or instrumentation so that infection may well have passed along the vas before the vasotomy was done.

In conclusion I submit that there is no evidence to suggest that division of the sheath of the vas as well as the vas itself is any more effective in preventing epididymitis and related complications than division of the vas alone, and that division of the vas alone is the preferable operation.

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Mr. **Ashton Miller** (Bristol): In the years 1951 and 1952 vasotomy was abandoned in the Bristol Urological Department as an accompaniment of prostatectomy; since then, bilateral vasotomy has been used in all cases.

INCIDENCE OF EPIDIDYMITIS

Total operations	= 390	Retropubic prostatectomy	366
		Transvesical prostatectomy	9
		Second-stage retropubic or transvesical	15
Without vasotomy	= 240	Epididymitis in hospital	27
		Epididymitis after discharge	8
With vasotomy	= 150	Infection in vasotomy scar	6
		Epididymitis	4

The incidence of epididymitis without vasotomy was therefore 15% (standard error ±4·0%) and with vasotomy it was 3% (standard error ±1·5%) under similar conditions. Attention is drawn to the high incidence of epididymitis after discharge from hospital in those patients who had no vasotomy.

Mr. **D. T. H. Paine** (Senior Registrar, St. Paul's Hospital): *Treatment of the Vasa Deferentia in Association with Operations on the Bladder: A Method of Interrupting them without Separate Incisions.*

The treatment of the vasa deferentia in association with operations on the bladder may be considered under the following headings:

(1) The necessity for vasal interruption.
(2) The optimum time for vasal interruption.
(3) The method of vasal interruption.
(4) The site of vasal interruption.

(1) *The necessity for vasal interruption.*—From Mr. Ashton Miller's remarks it would appear that interruption of the vasa is still indicated in spite of the advent of the antibiotics. One often hears surgeons say that the incidence of epididymitis has not increased since they gave up tying the vasa but are they not comparing their present figures with previous figures in which the vasa were tied, collected before the antibiotics were available?

An enormous literature grew up during the 1920s and 1930s and from this I find that the generally accepted incidence of clinical epididymitis following prostatectomy was around 21% (Crabtree and Brodny, 1930). This did not include late and recurrent cases after discharge from hospital which every urologist has encountered. If the epididymides are carefully examined palpable changes can be found in as many as 82% (Winsbury-White, 1922).

Interruption of the vasa, however, in the series of Crabtree and Brodny reduced the incidence to the region of 2% but was accompanied by a morbidity of its own in the region of 3·5%, such as local sepsis and hæmatoma.

The development of the various methods of treating the vasa is illustrated in Table I (after Abeshouse and Lerman, 1950).

TABLE I

Open vasoligation
(1) Perineal:
  (*a*) Proust, 1904
  (*b*) Young, 1905 (ejaculatory ducts)
(2) Inguinal:
  (*a*) Albarran, 1909
  (*b*) Burgess, 1932
(3) Suprapubic:
  (*a*) Sarnoff, 1931
(4) Scrotal:
  (*a*) Harberer, 1912
  (*b*) Morson, 1923
  (*c*) Darget (single scrotal mid-line incision)

Closed methods
(1) Colston, 1928
(2) Davis, 1933
(3) Way and White (with division) 1941

Vasoligation with division
(1) Keyes, 1931 (side-by-side ligation)
(2) Way and White, 1941

Vasoligation with partial resection
(1) Open: Goldstein, 1925
(2) Abeshouse, 1936 (with fascial interposition)

Vasal interruption first seems to have become fashionable between 1896 and 1909. Proust (1904) and Albarran (1909) both described its use in prostatectomy.

(2) *The optimum time for vasal interruption.*—Obviously it should be done before infection of the urine and before trauma of the posterior urethra have occurred. This is counsel of perfection as a very high proportion of cases present with already infected urine and it is often necessary to pass an instrument before a firm diagnosis can be made but Kreutzmann (1938) showed that cultures taken from the divided vasa were positive only where the urine was infected. He also showed that instrumentation

doubled the incidence of positive cultures. Therefore, where possible, interruption should be done immediately before instrumentation or at the latest immediately after it.

(3) *The method of vasal interruption.*—Simple ligation has been criticized over the decades on the grounds that complete interruption of the vas does not always occur and that regeneration often took place even with unabsorbable ligatures. Rolnick (1924) showed that in dogs regeneration could occur as early as two weeks after ligation.

Division of the vasa was therefore advocated. Keyes (1928, 1931) suggested side by side ligation like a gun barrel.

Colston (1928) and Alyea (1928) used a method of temporary ligation without a skin incision. The vas was frequently missed and on removal of the temporary ligatures an incidence of about 15% of epididymitis followed (McKay, 1928).

Morson in 1933 described injection of one in ten carbolic acid down the vas.

The inclusion of the sheath of the vas containing lymphatics is advocated by those believing in lymphatic or direct spread of the infection. Interposition of fascia or tunica vaginalis has also been used, notably by Abeshouse (1936).

(4) *The site of vasal interruption.*—Interruption of the ejaculatory ducts is not usually a practical proposition although Young used it in perineal operations on the prostate (Abeshouse and Lerman, 1950).

Ligation within the pelvis was done by Proust (1904) and Albarran (1909) but nowadays it is unpopular, surgeons seem to feel that if local infection at the site of interruption is going to occur they would rather have it outside the pelvis.

Harberer (1912) and Burgess (1932) advocated attacking the vasa in the inguinal region. Colston and Alyea did it with a temporary ligature as we have already seen while Way and White (1941) suggested a subcutaneous method using wire introduced through hollow needles. This method I feel must be rather tedious and more suited to the temperament of the ophthalmologist than the urologist.

Darget used a single mid-line scrotal incision at the junction of the penis and scrotum. It sounds difficult but in practice the vasa can quite readily be brought into the incision.

These methods are more or less simple but are liable to certain complications. These include local abscess in the lax tissues of the scrotum, hæmatoma from divided pampiniform veins and septic incisions which are not infrequently seen.

One disadvantage of the scrotal approach is the occasional occurrence of a urinary fistula through the cut end of the vas. One such case was recently seen at St. Paul's Hospital and several surgeons I have questioned have encountered them (*see* Hanley, 1945; Meade, 1947).

The scrotal approach is, of course, useful if preliminary catheter drainage or perineal drainage is being employed and with transurethral resection.

In 1948 I noticed how readily the cord could be brought into the lower abdominal skin incisions used for operations on the bladder and prostate. I therefore began interrupting the vas at the external ring through the abdominal incision. I was not aware that it had been described before but like everything else under the sun it is not new. Jacob Sarnoff described it in the *Medical Times* and *Long Island Medical Journal* in 1931. The method does not seem to have received much publicity, nor to be very widely used which is surprising since it is so satisfactory.

In most cases a few strokes with the points of the scissors expose the cord at the external inguinal ring. With practice the location of the cord with the thumb and forefinger becomes fairly easy as Sarnoff pointed out. In fat patients in the presence of a hernia it is not quite as easy but in these cases it may not be easy in the scrotum.

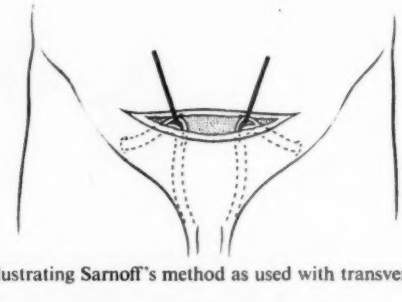

FIG. 1.—Illustrating Sarnoff's method as used with transverse incisions.

Fig. 1 shows how the method is used with transverse skin incisions but it can be used just as well in vertical incisions. Theoretical objections may be raised that exposing the vasa here opens up new tissue planes. This objection is not borne out in practice and in any case the inguinal region seems better able to deal with infection than the scrotum.

I have collected now 72 cases in which the vasa have been dealt with in this fashion. Of the 72, 2 cases developed definite epididymitis. One of these had pre-operative catheter drainage for seven days. The other, although having an uninfected urine, was reported by the pathologist to have a small abscess cavity in the removed adenomatous prostate.

There were 3 cases where a definite vasitis occurred down to the site of ligation on one side as evidenced by local pain, tenderness and swelling. In no case did suppuration occur nor was convalescence prolonged on account of it.

No other complications were encountered. I should like, therefore, to put the method forward for further consideration and trial by Members of the Section.

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Mr. H. P. Winsbury-White, Mr. J. C. Anderson, Mr. Marco Caine, Mr. Arthur Jacobs, Mr. A. Roche, Mr. H. G. Hanley, Mr. J. Gabe, and **Mr. D. T. H. Paine** took part in the subsequent discussion.

Vesico-ureteral Reflux [*Abridged*]

By D. ST.CLAIR L. HENDERSON, Ch.M., F.R.C.S.Ed.
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THERE are three factors involved in the protection of the uretero-vesical junction.

(*a*) The obliquity of insertion of the ureter, which is increased on distension of the bladder.

(*b*) The uretero-vesical valve. This is thicker in man than in most animals; its competence is increased on distension of the bladder by the intra-vesical pressure, and also due to the firm attachment of the mucous membrane of the bladder to the trigone.

(*c*) The trigone is the continuation of the longitudinal coat of the ureters and if Young and Wesson's (1921) interpretation of trigonal action is correct this is an important factor in preventing reflux on micturition.

There is no ureteric sphincter, and the intra-ureteral pressure is much too low to prevent reflux if the uretero-vesical mechanism is damaged.

In the cases investigated cystograms were taken, following vesical instillation of 10% sodium iodide, whilst filling, straining and during or immediately after micturition.

The conditions in which reflux may occur are:

(1) Congenital: certain cases of megalo-ureter.

(2) Inflammatory conditions: including tuberculous infection, Hunner's interstitial cystitis and bilharziasis.

(3) Lower urinary tract obstruction: may be associated with reflux.

(4) Neurogenic bladders: not present in all cases.

(5) Following trauma to the uretero-vesical junction: depending on its extent.

Ætiology.—(1) Neurogenic: the condition is not present in all neurogenic bladders (Talbot and Bunts, 1949) and the experimental evidence does not support this thesis (Barksdale and Baker, 1930).

(2) Antiperistalsis: in experimental reflux the intrapelvic pressure is equal to the intravesical.

(3) Urétère forcé: the ureter is surprised by a vesical contraction.

(4) Overdistension of the bladder: The adherence of the mucous membrane of the bladder to the trigone strengthens the normal uretero-vesical valve, and secondly, reflux is more frequent in the contracted bladder.

(5) Valve damage: Probably damage to the valve alone is insufficient to allow reflux if the other factors are acting normally, but with additional damage to the intramural ureter reflux may occur.

Several cases with illustrative slides demonstrating reflux were discussed and the cause of the reflux was attributed to damage involving some part of the uretero-vesical mechanism. The cases included ureteral meatotomy with diathermy to a neoplasm at the ureteric orifice, ureterocele treated by diathermy, reimplantation of the ureter, damage to the intramural ureter during diathermy to vesical neoplasms, chronic vesical infection and neurogenic bladder cases.

Symptoms.—Pain in the loin before or during micturition occurs in a small proportion of cases; it can be the presenting factor in bladder-neck obstruction. Disappearance of pain previously present is no indication that reflux has ceased. Ascending infection can readily occur. Regurgitation renal colic has been described by Lewis (1926, 1932); he attributes this to pelvic distension, but painless distension can be demonstrated in many reflux cases on micturition. A ureteric fistula in the presence of reflux may drain all the urine excreted by the patient.

Effects of reflux.—Dilatation of the ureter, commencing distally, is the initial change and in the presence of infection chronic pyelonephritis appears to follow. My impression is that the pyelographic changes on X-ray, even in the apparent absence of infection, are those of chronic pyelonephritis.

Hydronephrosis can improve in the presence of reflux if the cause is removed before permanent changes have taken place. Cystograms were demonstrated showing improvement in two cases: one case of uretero-vaginal fistula treated by reimplantation of the ureter in the bladder, and one case of ureteric calculus in a reimplanted ureter where ureterolithotomy was performed.

It is suggested that hydronephrosis occurs with reflux, apart from ureteric obstruction, only in cases where impaired bladder function results in frequent micturition and repeated insults to the kidney.

Prognosis.—Urinary infection is the deciding factor.

Treatment.—Reimplantation without achieving obliquity of the distal ureter is probably useless. Hutch's operation (1952) increases the length of the intravesical ureter and he reports seven successful cases in nine operations.

In conclusion the author thanked the President whose cases had provided the material for the investigation.

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Mr. Arthur Jacobs, **Mr. Hugh Donovan** and **Mr. D. St.Clair L. Henderson** took part in the subsequent discussion.